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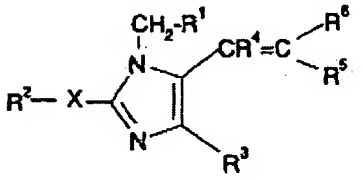
Remarks:
This application was filed on 06 - 08 - 1999 as a divisional application to the application mentioned under INID code 62.

(54) Imidazolyl-alkenoic acid

(57) Angiotensin II receptor antagonists having the formula (I):



(I)

which are useful in regulating hypertension and in the treatment of congestive heart failure, renal failure, and glaucoma, pharmaceutical compositions including these antagonists, and methods of using these compounds to produce angiotensin II receptor antagonism in mammals.

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Description

[0001] The present invention relates to new imidazolyl-alkenoic acids which are angiotensin II receptor antagonists and are useful in regulating hypertension induced or exacerbated by angiotensin II, and in the treatment of congestive heart failure, renal failure, and glaucoma. This invention also relates to pharmaceutical compositions containing these compounds and methods for using these compounds as antagonists of angiotensin II, as antihypertensive agents and as agents for treating congestive heart failure, renal failure, and glaucoma.

BACKGROUND OF THE INVENTION

[0002] The class of peptide pressor hormone known as angiotensin is responsible for a vasopressor action that is implicated in the etiology of hypertension in man. Inappropriate activity of the renin-angiotensin systems appears to be a key element in essential hypertension, congestive heart failure and in some forms of renal disease. In addition to a direct action on arteries and arterioles, angiotensin II (AII), being one of the most potent endogenous vasoconstrictors known, exerts stimulation on the release of aldosterone from the adrenal cortex. Therefore, the renin-angiotensin system, by virtue of its participation in the control of renal sodium handling, plays an important role in cardiovascular homeostasis.

[0003] Interruption of the renin-angiotensin system with converting enzyme inhibitors, such as captopril, has proved to be clinically useful in the treatment of hypertension and congestive heart failure (Abrams, W.B., et al., (1984), Federation Proc., 43, 1314). The most direct approach towards inhibition of the reninangiotensin system would block the action of AII at the receptor. Compelling evidence suggests that AII also contributes to renal vasoconstriction and sodium retention that is characteristic of a number of disorders such as heart failure, cirrhosis and complications of pregnancy (Hollenberg, N.K., (1984), J. Cardiovas. Pharmacol., 6, S176). In addition, recent animal studies suggest that inhibition of the renin-angiotensin system may be beneficial in halting or slowing the progression of chronic renal failure (Anderson, S., et al., (1985), J. Clin. Invest., 76, 612). Also, a recent patent application (South African Patent Application No. 87/01,653) claims that AII antagonists are useful as agents for reducing and controlling elevated intraocular pressure, especially glaucoma, in mammals.

[0004] The compounds of this invention inhibit, block and antagonize the action of the hormone AII, and are therefore useful in regulating and moderating angiotensin induced hypertension, congestive heart failure, renal failure and other disorders attributed to the actions of AII. When compounds of this invention are administered to mammals, the elevated blood pressure due to AII is reduced and other manifestations based on AII intercession are minimized and controlled. Compounds of this invention are also expected to exhibit diuretic activity.

[0005] Recognition of the importance of blocking and inhibiting the actions of AII has stimulated other efforts to synthesize antagonists of AII. The following references have disclosed imidazole derivatives which are described as having AII blocking activity and useful as hypotensive agents.

[0006] Furukawa et al, U.S. Patent 4,340,598 discloses imidazol-5-yl acetic acids and imidazol-5-yl-propanoic acids. Specifically, the discloser includes 1-benzyl-2-n-butyl-5-chloroimidazole-4-acetic acid and 1-benzyl-2-phenyl-5-chloroimidazole-4-propanoic acid.

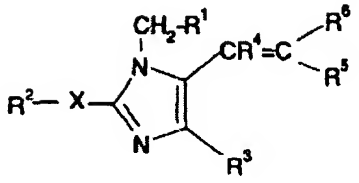
[0007] Furukawa, et al., U.S. Patent 4,355,040 discloses substituted imidazole-5-acetic acid derivatives. A compound specifically disclosed is 1-(2-chlorobenzyl)-2-n-butyl-4-chloroimidazole-5-acetic acid.

[0008] Carini et al. in EP 253,310 disclose certain imidazolylpropenoic acids. Two intermediates described in this patent are ethyl 3-[1-(4-nitrobenzyl)-2-butyl-4-chloroimidazol–5-yl]propenoate and ethyl 3-[2-butyl-4-chloro-1-(4-aminobenzyl)imidazol-5-yl]propenoate.

[0009] Also, Wareing, in PCT/EP 86/00297, discloses as intermediates certain imidazolylpropenoate compounds. On page 62, Formula (CX) is ethyl 3-[1-(4-fluorophenyl)-4-isopropyl-2-phenyl-1H-imidazol-5-yl]-2-propenoate.

DESCRIPTION OF THE INVENTION

[0010] The present invention relates to blockers of angiotensin II receptors represented by the following Formula (I):



(I)

in which:

R^1 is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_1-C_4alkyl, nitro, CO_2R^7,tetrazol-5-yl, C_1-C_4alkoxy, hydroxy, SC_1-C_4alkyl, SO_2NHR^7, $NHSO_2R^7$, SO_3H, $CONR^7R^7$, CN, SO_2C_1-C_4alkyl, or C_nF_{2n+1}, wherein n is 1-3;
R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_6cycloalkyl, or $(CH_2)_{0-6}$phenyl unsubstituted or substituted by one to three substituents selected from C_1-C_4alkyl nitro, Cl, Br, F, I, hydroxy, C_1-C_4alkoxy, NR^7R^7, CO_2R^7, CN, or $CONR^7R^7$;
X is a single bond, S, or O;
R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, $COOR^7$, $CONR^7R^7$, NO_2, or C_nF_{2n+1}, wherein n is 1-3;
R^4 and R^5 are independently hydrogen, C_1-C_6alkyl, thienyl-Y-, furyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, pyridyl-Y-, or tetrazolyl-Y-, except that R^4 and R^5 are not both selected from hydrogen and C_1-C_6alkyl and each heterocyclic ring is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, Cl, Br, F, I, NR^7R^7,CO_2R^7,SO_2NHR^7 ,SO_3H, or $CONR^7R^7$;
Y is a single bond, O, S, or C_1-C_6alkylene which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO_2, CF_3, C_1-C_4alkyl, C_1-C_4alkoxy, CN, or CO_2R^7;
R^5 is -Z-$COOR^8$ or -Z-$CONR^7R^7$;
Z is a single bond, vinyl, -CH_2-O-CH_2-, methylene optionally substituted by C_1-C_4alkyl, one or two benzyl groups, thienylmethyl, or furylmethyl, or -C(O)NHCHR^9-, wherein R^9 is H, C_1-C_6alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;
each R^7 independently is hydrogen, C_1-C_4alkyl, or $(CH_2)_m$phenyl, wherein m is 0-4; and
R^8 is hydrogen, C_1-C_6alkyl, or 2-di(C_1-C_6alkyl)-amino-2-oxoethyl; or a pharmaceutically acceptable salt thereof.

[0011] Preferably, one of R^4 and R^5 is hydrogen or C_1-C_6alkyl.

[0012] Preferred compounds of this invention are represented by Formula (I) when:

R^1 is phenyl unsubstituted or substituted by one to three substituents selected from chloro, fluoro, trifluoromethyl, nitro, methyl, methoxy, hydroxy, sulfamido, carboxy, carboC_1-C_4alkoxy, carbamoyl, cyano, or tetrazol-5-yl;
X is a single bond;
R^2 is C_2-C_8alkyl;
R^3 is hydrogen, chloro, fluoro, or trifluoromethyl;
R^4 is hydrogen or C_1-C_6alkyl;
R^5 is thienylmethyl, furylmethyl, imidazolylmethyl, or pyridylmethyl, each of which is optionally substituted by methyl or methoxy; and
R^6 is COOH, $COOC_{1-2}$alkyl, or $CONH_2$; or a pharmaceutically acceptable salt thereof.

[0013] The E isomers (trans stereochemistry of the R^6 group and imidazole group) are generally more active and thus, are preferred over the Z isomers (cis).

[0014] As used herein, the terms alkyl, alkenyl, alkoxy and alkynyl mean carbon chains which are branched or unbranched with the length of the chain determined by the descriptor preceding the term.

[0015] Particular compounds of the invention include, but are not limited to, the following:

(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-furyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-thienyl)methyl-2-propenoic acid,

(E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-imidazolyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(2-cyanophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methoxy-2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(2,3-dichlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(4-carboxy-2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(4-carboxy-3-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-hexyl-1-(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, and
(E)-3-[2-n-butyl-1-[(2-trifluoromethylphenyl)-methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or a pharmaceutically acceptable salt thereof.

[0016] The invention also relates to pharmaceutical compositions comprising a pharmaceutical carrier and an effective amount of a compound of Formula (I).

[0017] Also included in the present invention are methods for antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I). methods of producing antihypertensive activity and methods of treating congestive heart failure, glaucoma, and renal failure by administering these compounds are also included in this invention.

[0018] The compounds of this invention are prepared by procedures described herein and illustrated by the examples. Reagents, protecting groups and functionality on the imidazole and other fragments of the molecule must be consistent with the proposed chemical transformations. Steps in the synthesis must be compatible with the functional groups and the protecting groups on the imidazole and other parts of the molecule.

[0019] The starting materials, 2-R^2X-imidazole, are known to the art (J. Org. Chem. 45:4038, 1980) or are synthesized by known procedures. For example, imidazole is converted to 2-n-butylimidazole by reacting imidazole with triethylorthoformate and p-toluenesulfonic acid to give 1-diethoxyorthoamide imidazole and then treating with n-butyl lithium to give the 2-lithium derivative of the orthoamide and alkylating with n-butyl iodide in a suitable solvent, such as tetrahydrofuran (THF).

[0020] The following procedure is useful for the preparation of compounds of Formula (I) particularly where R^1 is 2-chlorophenyl, R^2 is n-butyl, R^3 is hydrogen, chloro, or CF_3, R^4 is hydrogen, R^5 is as described in Formula (I), R^6 is $COOR^8$ and R^8 is hydrogen, methyl, or ethyl.

[0021] The 1-R^1CH_2-group is incorporated onto the 2-R^2X-imidazole by known procedures, for example, by reaction with an R^1-CH_2 halide, mesylate or acetate, such as 2-chlorobenzyl bromide, in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable acid acceptor, such as sodium alkylate, potassium or sodium carbonate, or a metal hydride, preferably sodium hydride at a reaction temperature of 25°C to 100°C, preferably 50°C. The resulting 1-R^1CH_2-2-R^2X imidazole is hydroxymethylated in the 5-position, for example, by reacting with formaldehyde in the presence of sodium acetate in acetic acid to provide the 1-R^1CH_2-2-R^2X-5-hydroxymethylimidazole intermediates.

[0022] Alternatively, the 1-R^1CH_2-2-R^2X-5-hydroxymethylimidazole intermediates are prepared by reacting an imido ether, R^2-C(=NH)-O-alkyl, such as valeramidine methyl ether, with dihydroxyacetone in liquid ammonia under pressure to give 2-R^2-5-hydroxymethylimidazole. This intermediate is reacted with acetic anhydride to give 1-acetyl-5-acetoxymethyl-2-R^2-imidazole. The diacetate intermediate is N-alkylated, for example, using 2-chlorobenzyl triflate and the resulting 1-R^1CH_2-2-R^2-5-acetoxymethylimidazole is treated with aqueous base, such as 10% sodium hydroxide solution, to give the 1-R^1CH_2-2-R^2-5-hydroxymethylimidazole intermediate.

[0023] Alternatively, the 2-R^1S-imidazole compounds are prepared by the following procedure. Benzylamines, substituted by one to three substituents selected from halo, C_{1-4}alkyl, C_{1-4}alkoxy, CN, NO_2, CF_3, CO_2C_{1-6}alkyl, SC_{1-4}alkyl, or SO_2C_{1-4}alkyl, are alkylated with a C_{1-6}alkyl chloroacetate, for example methyl chloroacetate, in the presence of a base, such as triethylamine, in a suitable solvent, such as dimethylformamide. The resulting alkylaminoalkyl ester compounds are N-formulated with formic acid in the presence of a suitable solvent, such as xylenes, followed by C-formulation of the carbon alpha to both the amino and the ester groups. Reaction of this intermediate with acidic thiocyanate, preferably potassium thiocyanate, in an inert organic solvent, such as C_{1-4}alkyl alcohol produces 1-RCH_2-2-mercapto-5-alkanoate ester imidazole compounds. The free thio group of the ester imidazole is reacted with a halo-R^{10} compound, wherein R^{10} is C_{2-10}alkyl, C_{3-10}alkenyl, C_3-C_{10}alkynyl, C_3-C_6cycloalkyl or an optionally substituted $(CH_2)_{0-8}$Ph, preferably propyl bromide, in the presence of a suitable base, such as sodium carbonate, in an appropriate solvent, such as ethyl acetate. The ester is reduced to the hydroxymethyl-imidazole intermediate by reduction with a suitable reagent, preferably diisobutyl aluminum hydride, in an appropriate solvent, such as tetrahydrofuran, at a temperature of -78°C to 25°C, preferably at less than -10°C.

[0024] The hydroxymethyl group of the hereinbefore prepared intermediate is oxidized to an aldehyde by treatment

with a suitable reagent, such as anhydrous chromic acid-silica gel in tetrahydrofuran or, preferably, with activated manganese dioxide, in a suitable solvent, such as benzene or toluene, or preferably methylene chloride, at a temperature of 25°C to 140°C, preferably at 25°C. The 1-R^1CH_2-2-R^2X-imidazol-5-carboxaldehydes are reacted with an appropriate phosphonate, such as those listed in Table I (Examples 2-5). The phosphonates are prepared, for example, from trialkyl phosphonoacetates by alkylation with an appropriate halide, mesylate or acetate in the presence of a suitable base, such as sodium hydride, in a suitable solvent, preferably glyme at a reaction temperature of 25°C to 110°C, preferably at 55°C, to provide, for example, the phosphonates listed in Table I. The reaction of the imidazol-5-carboxaldehydes with the phosphonates is performed in the presence of a suitable base, such as a metal alkoxide, lithium hydride or preferably sodium hydride, in a suitable solvent, such as ethanol, methanol, ether, dioxane, tetrahydrofuran, or preferably glyme, at a reaction temperature of 10°C to 50°C, preferably at 25°C, to provide a variable mixture of trans and cis, e.g., (E) and (Z), 1-R^1CH_2-2-R^2X-5-CH=C(R^5)-(COO-alkyl)-imidazoles. These isomers are readily separated by chromatography over silica gel in suitable solvent systems, preferably hexane in ethyl acetate mixtures. The esters are hydrolyzed to the acids, 1-R^1-CH_2-2-R^2X-5-CH=C(R^5)COOH-imidazoles, using bases , such as potassium hydroxide, lithium hydroxide or sodium hydroxide, in a suitable solvent system, such as, for example, aqueous alcohols or diglyme. The trans and cis structures of the acids are readily determined by NMR by the NOE protocol, as well as by the biological activities since, generally, the trans (E) isomeric acids are the more potent isomers.

[0025] Alternatively, the 1-R^1CH_2-2-R^2X-imidazol-5-carboxaldehydes are prepared by the following procedure. Starting 2-R^2X-imidazol-4-carboxaldehydes are reacted with an N-alkylating protecting reagent, such as chloromethyl pivalate (POM-Cl), in the presence of a base, such as dimethylformamide, at a temperature of 20°C to 50°C, preferably at 25°C, to give N-alkylation (e.g., POM-derivation) on the least hindered nitrogen atom of the imidazole nucleus. The 1-R^1CH_2-group is incorporated onto the imidazole by N-alkylation of the above prepared aldehyde with a halomethylbenzene compounds, such as methyl 4-bromomethyl-3-chlorobenzoate, at a temperature of 80°C to 125°C, preferably at 100°C. The protecting group on the 3-nitrogen of the imidazole ring is removed by base hydrolysis, for example using a biphasic mixture of ethyl acetate and aqueous sodium carbonate, to give 1-R^1CH_2-2-R^2X-imidazole-5-carboxaldehyde compounds. The Formula (I) compounds can be prepared from these 5-carboxaldehyde compounds by the methods described above.

[0026] Compounds of Formula (I), wherein R^6 is $COOR^8$, R^1, R^2, R^3, R^4 and R^5 are as described in Formula (I), and R^8 is H, methyl or ethyl, are also prepared by the following procedure.

[0027] The 2-R^2X-imidazole starting materials are reacted with trimethylsilylethoxymethyl (SEM) chloride to give 1-(trimethylsilyl) ethoxymethyl-2-R^2-imidazole. The reaction is carried out, for example, in the presence of sodium hydride in a solvent such as dimethylformamide. The 5-tributyltin derivatives are prepared by lithiation with, for example, butyllithium in a suitable solvent, preferably diethyl ether, followed by treatment of the lithio imidazole derivative with a tributyltin halide, preferably tri-N-butyltin chloride, at -10°C to 35°C, preferably at 25°C. The 1-SEM-2-R^2-5-tributyltinimidazole is coupled with an α,β-unsaturated acid ester having a leaving group on the β-position, such as a halide or trifluoromethanesulfonyloxy group, for example, $BrCR^4$=C(R^5)(COOalkyl), in the presence of a phosphine ligand, such as bis(diphenylphosphino)propane, or triphenyiphosphine and a palladium (II) compound, or preferably tetrakis(triphenylphosphine)-palladium(0), with or without a base, such as tributylamine, at a temperature of 50°C to 150°C, preferably at 120°C. Both the (E) and (Z) olefinic isomers are prepared by this procedure, and the isomeric esters are readily separated by chromatography over silica gel. The 1-SEM group from the (E) and (Z) isomers is hydrolyzed with acid, for example, aqueous hydrochloric, in a suitable alcoholic solvent, such as methanol or ethanol, and the 1-unsubstituted imidazole derivatives are converted to the 1-t-butoxycarbonyl (t-BOC) imidazoles with di-t-butyl dicarbonate (Hoppe-Seyler's Z. Physiol. Chem., (1976), 357, 1651). The t-BOC esters are alkylated and hydrolyzed with, for example, 2-chlorobenzyl-O-triflate in the presence of a suitable base, preferably diisopropylethylamine, in a suitable solvent, preferably methylene chloride, to afford the 1-(2-chlorophenyl)methylimidazole derivatives (esters). The (E) and (Z) isomers are hydrolyzed to the (E) and (Z) acids by the method described above.

[0028] Compounds of Formula (I) are also prepared by the following procedure. The 1-R^1CH_2-2-R^2X-imidazole-5-carboxaldehydes, prepared as described above, are reacted with a substituted half-acid, half-ester derivative of a malonate, such as ethyl 2-carboxy-3-(2-thienyl)propionate, in the presence of a base, such as piperidine, in a suitable solvent, such as toluene, at a temperature of 80°C to 110°C, preferably at 100°C. The resulting 1-R^1CH_2-2-R^2X-5-CH=C(R^5)COO alkylimidazoles are hydrolyzed to the corresponding Formula (I) acid compounds by alkaline hydrolysis as described above.

[0029] Compounds of Formula (I) in which R^1 is 2-chlorophenyl, R^2 is n-butyl, R^3 is H, Cl, or CF_3, R^4 is methyl, R^5 is as described in Formula (I), R^6 is $COOR^8$ and other parameters are as described above are prepared as follows. The 1-R^1CH_2-2-R^2X-imidazol-5-carboxaldehydes, prepared as described above, are converted to the corresponding alcohols with an organo-metallic derivative or Grignard reagent, preferably methyl lithium, in a suitable solvent, such as tetrahydrofuran. The alcohol is oxidized, for example, using manganese dioxide to give the ketone. The olefinic esters are prepared from the ketone by reaction with appropriate phosphonates to give the (E) and/or (Z) isomers which are readily separated. The acids are prepared from the esters by alkaline hydrolysis as described above.

[0030] Compounds of Formula (I) in which R^3 is H, Cl, CH_2OH, or CF_3 are prepared as follows. The 1-R^1-CH_2-2-R^2X-imidazol-5-carboxaldehydes are treated with the lithium derivatives of a substituted ethyl or methyl ester. These lithio derivatives are prepared from the reaction of lithium diisopropylamide in a suitable solvent, preferably tetrahydrofuran, with an acid ester, such as ROOC-CH_2-Y-(2-thienyl), to generate the α-lithio derivatives at -78°C to -10°C, preferably at -78°C, which are then treated with the imidazol-carboxaldehyde. The intermediate β-hydroxy group of the imidazol ester is converted to a mesylate or an acetate and the mesylate, or preferably the acetate, is heated in a suitable solvent, such as toluene, with one to two equivalents of 1,8-diazo-bicyclo[5.4.0]undec-7-ene, at 50 to 110°C, preferably at 80°C, to afford ester compounds of Formula (I) such as 3-(imidazol-5-yl)-2-(2-thienyl)methyl-2-propenoic acid esters. The (E) isomer is the predominate olefinic isomer. The acids are prepared from the esters by the method described above. Compounds of Formula (I), wherein R^1 is 2-chlorophenyl, R^2 is n-butyl, R^3 is H, Cl, CF_3, or CH_2OH, R^4 is H, R^5 is heterocyclic or a substituted heterocyclic group as described in Formula (I) and R^6 is COOH, may be prepared by heating 1-R^1-CH_2-2-R^2X-imidazol-5-carboxaldehydes at 50°C to 180°C, preferably at 140°C, with an appropriate substituted heterocyclic acetic acid and with acetic anhydride and potassium carbonate to provide unsaturated acids of formula (I) such as 3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-R^5-2-propenoic acid. The trans olefinic acid is the principal product.

[0031] Compounds of Formula (I) in which R^6 is Z-COOR^8 where Z is an optionally substituted methylene group are prepared by reducing the trans or (E) isomers of 3-(imidazol-5-yl)-2-propenoic acid esters (prepared as described above) with an appropriate hydride reagent, preferably diisobutylaluminum hydride, in a suitable solvent, such as tetrahydrofuran, to provide the unsaturated alcohol compounds. These compounds are reacted with ethyl chloroformate, for example, with a base, preferably triethylamine, in a suitable solvent, such as tetrahydrofuran, to give 5-EtOOCOCH_2CR^5=CR^4-imidazols which are reacted with carbon monoxide in the presence of a phosphine ligand, preferably triphenyl-phosphine with palladium (II) acetate, in a suitable solvent, preferably tetrahydrofuran, at a temperature of 25°C to 100°C, preferably at 40°C, to give the 5-EtOOCCH_2CR^5=CR^4-imidazols. The corresponding acids are prepared from these ethyl esters by base hydrolysis as described above.

[0032] Compounds of Formula (I) in which Z is -CH_2COOR^8 having additional substitution on the carbon α to the carboxylate group are prepared by converting 5-EtOOCH_2CR^5=CH^4-imidazols to the lithium derivative of the ester with a lithium dialkylamide, preferably lithium diisopropylamide, and then treating with an alkylating agent, such as methyl halide, benzyl bromide, or heterocyclic methyl halide, to provide the mono-alkylated product compounds or the dialkylated product compounds. The acid compounds are prepared from the esters by base hydrolysis.

[0033] Compounds of Formula (I) in which R^6 is Z-COOR^8 where Z is -CH_2-O-CH_2- are prepared from unsaturated alcohol compounds, which had been obtained by the reduction of the Formula (I) propenoic acid esters. The alcohol is reacted with an appropriate hydride reagent, such as sodium hydride, in a suitable solvent, such as glyme, followed by reaction with an alkylating reagent, such as methyl bromoacetate, to give 5-MeOOCCH_2-O-CH_2CR^5=CR^4-imidazols. The corresponding acids are prepared from these esters by base hydrolysis as described above.

[0034] Compounds of Formula (I) in which R^6 is Z-COOR^8 where Z is —C(O)NHCHR^9- are prepared from the Formula (I) propenoic acid compounds. These acids are reacted with an appropriately substituted amino acid, such as glycine methyl ester hydrochloride or phenylalanine methyl ester hydrochloride, in the presence of an amide-forming reagent, such as N-hydroxysuccinimide and dicyclohexylcarbodiimide, in the presence of a base, for example triethylamine, in a suitable solvent, such as tetrahydrofuran, at a temperature of 20°C to 50°C, preferably at 35°C. The 5-C_1-$_4$alkylOOCCHR^9NHC(O)-CH_2CR^5-CR^4-imidazols are converted to their corresponding acids by base hydrolysis as described above.

[0035] Compounds of Formula (I) in which the R^1 substituent is substituted by hydroxy are formed from Formula (I) compounds in which the R^1 group is substituted by C_1-C_4alkoxy using an ether-cleaving reagent, such as boron tribromide or hydrobromic acid.

[0036] Compounds of Formula (I) in which the R^1 substituent is substituted by carboxy are formed from Formula (I) compounds in which the R^1 group is substituted by CO_2C_1-C_4alkyl using basic hydrolysis or ethanol, or using acidic hydrolysis, such as aqueous hydrochloric acid.

[0037] Compounds of Formula (I) in which the R^1 substituent is substituted by a tetrazol-5-yl group are prepared from the corresponding carboxy compounds. For example, Formula (I) acid compounds are reacted with a halogenating agent, such as thionyl chloride, in a suitable solvent, for example benzene, to give the corresponding acid halide compounds. The acid halides are then converted to primary amide compounds in a reaction with concentrated ammonia. Subsequent dehydration of the amides with oxalyl chloride/dimethylformamide in acetonitrile/dimethylformamide yields and the nitrile compounds, which are the immediate precursors to the Formula (I) tetrazole compounds. Tetrazole formation is accomplished by reacting the nitriles with azide, preferably aluminum azide prepared in situ by the reaction of sodium azide with aluminum chloride, in a suitable solvent, for example tetrahydrofuran. The Formula (I) compounds in which R^6 is —Z-CO_2H are prepared from these Formula (I) tetrazole ester compounds by basic hydrolysis as described above.

[0038] Pharmaceutically acceptable acid addition salts of compounds of Formula (I) are formed with appropriate

organic or inorganic acids by methods known in the art. For example, the base is reacted with a suitable inorganic or organic acid in an aqueous miscible solvent such as ethanol with isolation of the salt by removing the solvent or in an aqueous immiscible solvent when the acid is soluble therein, such as ethyl ether or chloroform, with the desired salt separating directly or isolated by removing the solvent. Representative examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylene-salicyclic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicyclic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexyl-sulfamic, phosphoric and nitric acids.

[0039] Pharmaceutically acceptable base addition salts of compounds of Formula (I) in which R^8 is H are prepared by known methods from organic and inorganic bases, including nontoxic alkali metal and alkaline earth bases, for example, calcium, lithium, sodium, and potassium hydroxide; ammonium hydroxide, and nontoxic organic bases, such as triethylamine, butylamine, piperazine, and (trihydroxymethyl)-methylamine.

[0040] Angiotensin II antagonist activity of the compounds of Formula (I) is assessed by in vitro and in vivo methods. In vitro antagonist activity is determined by the ability of the compounds to compete with ^{125}I-angiotensin II for binding to vascular angiotensin II receptors and by their ability to antagonize the contractile response to angiotensin II in the isolated rabbit aorta. In vivo activity is evaluated by the efficacy of the compounds to inhibit the pressor response to exogenous angiotensin II in conscious rats and to lower blood pressure in a rat model of renin dependent hypertension.

Binding

[0041] The radioligand binding assay is a modification of a method previously described in detail (Gunther et al., Circ. Res. 47:278, 1980). A particular fraction from rat mesenteric arteries is incubated in Tris buffer with 80 pM of ^{125}I-angiotensin II with or without angiotensin II antagonists for 1 hour at 25°C. The incubation is terminated by rapid filtration and receptor bound ^{125}I-angiotensin II trapped on the filter is quantitated with a gamma counter. The potency of angiotensin II antagonists is expressed as the IC_{50} which is the concentration of antagonist needed to displace 50% of the total specifically bound angiotensin II. Exemplary of the IC_{50} of compounds of the invention (E isomers) is about 0.1 nM to about 100 μM.

Aorta

[0042] The ability of the compounds to antagonize angiotensin II induced vasoconstriction is examined in the rabbit aorta. Ring segments are cut from the rabbit thoracic aorta and suspended in organ baths containing physiological salt solution. The ring segments are mounted over metal supports and attached to force displacement transducers which are connected to a recorder. Cumulative concentration response curves to angiotensin II are performed in the absence of antagonist or following a 30-minute incubation with antagonist. Antagonist disassociation constants (K_B) are calculated by the dose ratio method using the mean effective concentrations. Exemplary of the K_B of compounds of the invention (E isomers) is about 0.1 nM to about 30 μM.

Inhibition of pressor response to angiotensin II in conscious rats

[0043] Rats are prepared with indwelling femoral arterial and venous catheters and a stomach tube (Gellai et al, Kidney Int. 15:419, 1979). Two to three days following surgery the rats are placed in a restrainer and blood pressure is continuously monitored from the arterial catheter with a pressure transducer and recorded on a polygraph. The change in mean arterial pressure in response to intravenous injections of 250 mg/kg angiotensin II is compared at various time points prior to and following the administration of the compounds intravenously or orally at doses of 0.1 to 300 mg/kg. The dose of compound needed to produce 50% inhibition of the control response to angiotensin II (IC_{50}) is used to estimate the potency of the compounds. The IC_{50} of (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid is 3.60 mg/kg i.v. and 44.00 mg/kg orally.

Antihypertensive activity

[0044] The antihypertensive activity of the compounds is measured by their ability to reduce mean arterial pressure in conscious rats made renin-dependent hypertensive by ligation of the left renal artery (Cangiano et al., J. Pharmacol. Exp. Ther. 208:310, 1979). Renal artery ligated rats are prepared with indwelling catheters as described above. Seven to eight days following renal artery ligation, the time at which plasma renin levels are highest, the conscious rats are placed in restrainers and mean arterial pressure is continuously recorded prior to and following the administration of the compounds intravenously or orally. The dose of compound needed to reduce mean arterial pressure by 30 mm Hg (IC_{50}) is used as an estimate of potency. The IC_{50} of (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid is 1.80 mg/kg i.v. and 8.0 mg/kg orally.

[0045] The intraocular pressure lowering effects employed in this invention may be measured by the procedure described by Watkins, et al., J. Ocular Pharmacol., 1 (2): 161-168 (1985).

[0046] The compounds of Formula (I) are incorporated into convenient dosage forms, such as injectable preparations, or for orally active compounds, capsules or tablets. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid, such as an ampoule, or an aqueous or nonaqueous liquid suspension.

[0047] For topical ophthalmologic administration, the pharmaceutical compositions adapted include solutions, suspensions, ointments, and solid inserts. Typical pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, and water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving wetting, and bodying agents, as for example, polyethylene glycols; antibacterial components, such as quaternary ammonium compounds; buffering ingredients, such as alkali metal chloride; antioxidants, such as sodium metabisulfite; and other conventional ingredients, such as sorbitan monolaurate.

[0048] Additionally, suitable ophthalmic vehicles may be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems.

[0049] The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

[0050] The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral, parenteral, or topical products.

[0051] Doses of the compounds of Formula (I) in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity selected from the range of 0.01 - 200 mg/kg of active compound, preferably 1 - 100 mg/kg. The selected dose is administered to a human patient in need of angiotensin II receptor antagonism from 1-6 times daily, orally, rectally, topically, by injection, or continuously by infusion. Oral dosage units for human administration preferably contain from 1 to 500 mg of active compound. Preferably, lower dosages are used for parenteral administration. Oral administration, at higher dosages, however, also can be used when safe and the active compound in an amount selected from 0.0001 to 0.1 (w/v%), preferably from 0.0001 to 0.01. As a topical dosage unit form, an amount of active compound from between 50 ng to 0.05 mg, preferably 50 ng to 5 µg, is applied to the human eye.

[0052] The method of this invention of antagonizing angiotensin II receptors in mammals, including humans, comprises administering to a subject in need of such antagonism an effective amount of a compound of Formula (I). The method of this invention of producing antihypertensive activity and the method of treating congestive heart failure, glaucoma, and renal failure comprise administering a compound of Formula (I) to a subject in need thereof an effective amount to produce said activity.

[0053] Contemplated equivalents of Formula (I) compounds are compounds otherwise corresponding thereto wherein substituents have been added to any of the unsubstituted positions of the Formula (I) compounds provided such compounds have the pharmaceutical utility of Formula (I) compounds.

[0054] The following examples illustrate preparation of compounds and pharmaceutical compositions of this invention. The examples are not intended to limit the scope of this invention as described hereinabove and as claimed below.

Example 1

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0055]

(i) 2-n-butyl-1-(2-chloro-phenyl)methyl-1H-imidazole

Imidazole was converted to the 1-diethoxyorthoamide derivative by the method of Curtis and Brown, J. Org. Chem., (1980), 45, 20. Imidazole (12.8 g, 0.19 mol) and 118.4 g (0.8 mol) of triethylorthoformate were reacted in the presence of 1 g of p-toluenesulfonic acid to give 20.6 (61%), bp 65-70°C (0.1 mm) of 1-diethoxyorthoamide imidazole. This product (24.0 g, 0.14 mol) was dissolved in dry tetrahydrofuran (250 mL), cooled to -40°C and n-butyl lithium (0.14 mol, 56.4 mL of 2.5 M in hexane) was added at -40°C to -35°C. After 15 minutes n-butyl iodide (31.1 g, 0.169 mol) was added at -40°C, and the reaction was stirred overnight at ambient temperature. The reaction was

partitioned between ether and 0.3 N hydrochloric acid, and the organic layer was repeatedly extracted with dilute hydrochloric acid. The combined aqueous extracts were neutralized with sodium bicarbonate solution, extracted with methylene chloride, dried over magnesium sulfate and concentrated. A flash distillation on a Kugelrohr apparatus provided 14.8 g (85%) of 2-n-butylimidazole.

2-n-Butylimidazole (9.7 g, 0.078 mol) was dissolved in methanol (50 mL) and added dropwise to a solution of sodium methoxide (from sodium hydride (2.31 g, 0.0934 mol) in methanol (250 mL)). After one hour the solution was evaporated to dryness, and the sodium salt was taken up in dry dimethylformamide (150 mL) and 2-chlorobenzyl bromide (16.3 g, 0.079 mol) was added. The mixture was heated at 50°C for 17 hours under argon, poured onto ice water and the product was extracted into ethyl acetate. The extract was washed, dried, and concentrated to give 18.5 g of crude product which was chromatographed over silica gel with 2:1 ethyl acetate/hexane to provide 11.9 g (61%) of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazole as an oil. Thin layer chromatography on silica gel with 4:1 ethyl acetate/hexane gave an R_f value of 0.59.

(ii) 2-n-butyl-1-(2-chlorophenyl)methyl-5-hydroxymethyl-1H-imidazole

Method 1 A mixture of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazole (95.5 g, 0.384 mol), 37% formaldehyde (500 mL), sodium acetate (80 g) and acetic acid (60 mL) was heated to reflux for 40 hours under argon. The reaction was concentrated in vacuo, and the residue was stirred with 500 mL of 20% sodium hydroxide solution for 4 hours, diluted with water and extracted with methylene chloride. The extract was washed, dried, and concentrated. The crude product (117 g) was flash chromatographed over 600 g of silica gel with a gradient of ethyl acetate to 10% of methanol in ethyl acetate to give 8.3 g of starting material, 24.5 g of a mixture of starting material and product, and 44 g (41%) of 2-n-butyl-1-(2-chlorophenyl)-methyl-5-hydroxymethyl-1H-imidazole; mp 86-88°C (from ethyl acetate). Further elution provided the bis (4,5-hydroxymethyl) derivative; mp 138-140°C (from ethyl acetate).

Method 2 A mixture of valeramidine methyl ether hydrochloride (250 g, 1.66 mol) and dihydroxyacetone (150 g, 0.83 mol) dissolved in liquid ammonia was allowed to stand overnight at room temperature in a pressure vessel, and then heated at 65°C for 4 hours at 375 psi. The ammonia was allowed to evaporate, and the residue was dissolved in methanol (3L). The resulting slurry was refluxed with added acetonitrile (1L). The solution was decanted from the solid ammonium chloride while hot. This procedure was repeated, and the combined acetonitrile extracts were treated with charcoal, filtered hot and the filtrate was concentrated in vacuum to give the dark oil, 2-n-butyl-5-hydroxymethylimidazole (253 g, 1.63 mol, 98%).

This crude alcohol (253 g) was treated with acetic anhydride (400 mL) at -15°C and then was allowed to warm to ambient temperature with stirring, and then stirred an additional 19 hours. The acetic anhydride was evaporated at reduced pressure, the residue taken up in methylene chloride, and the organic phase was washed with 5% sodium bicarbonate solution and water. The extract was dried over sodium sulfate and concentrated to give 323 g (83%) of 1-acetyl-4-acetoxymethyl-2-n-butylimidazole.

This diacetate was N-alkylated by the following procedure. To a solution of triflic anhydride (120 mL, 0.71 mol) in methylene chloride (200 mL) at -78°C under argon was added a solution of diisopropyl ethylamine (128 mL, 0.73 mol) and 2-chlorobenzyl alcohol (104 g, 0.72 mol) in methylene chloride (350 mL) over a period of 20 minutes. After being stirred an additional 20 minutes at -78°C, this solution was then treated with 1-acetyl-4-acetoxymethyl-2-n-butylimidazole (146 g, 0.61 mol) dissolved in methylene chloride (300 mL) over a 20-minute interval. The mixture was then stirred at ambient temperature for 18 hours and the solvents were evaporated, The residual 2-n-butyl-5-acetoxymethyl-1-(2-chlorophenyl)methyl-1H-imidazole was used without purification for the hydrolysis of the acetate group.

A solution of crude 2-n-butyl-5-acetoxymethyl-1-(2-chlorophenyl)methyl-1H-imidazole (250 g) in methanol (200 mL) was treated with 10% sodium hydroxide solution (700 mL) and the mixture was heated on a steam bath for 4 hours. After cooling, methylene chloride was added, the organic phase was separated, washed with water, dried and concentrated. The residue was dissolved in ether, cooled, and seeded to give the crude product. Recrystallization from ethyl acetate gave 176 g of 2-n-butyl-1-(2-chlorophenyl)methyl-5-hydroxymethyl-1H-imidazole; mp 86-88°C. This material was identical in all respects to the product prepared by Method 1.

(iii) 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde

A solution of 2-n-butyl-1-(2-chlorophenyl)methyl-5-hydroxymethyl-1H-imidazole (5.4 g, 0.0194 mol) in toluene (25 mL) was added to a suspension of activated manganese dioxide (27 g) in methylene chloride (325 mL). The suspension was stirred at room temperature for 17 hours. The solids were filtered and the filtrate concentrated and

flash chromatographed over silica gel with 6:4 hexane/ethyl acetate to afford 4.16 g (78%) of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde, as an oil. NMR and IR were consistent with the structure.

(iv) (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

Method A (a) trimethyl 3-(2-thienyl)-2-phosphonopropionate

To a solution of 2-thiophenemethanol (2.28 g, 0.02 mol) in carbon tetrachloride (25 mL) was added triphenylphosphine (6.81 g, 0.026 mol), and the solution was refluxed for 3 hours. The cooled reaction mixture was diluted with hexane (60 mL), chilled and filtered. The concentrated filtrate (4.6 g) was flash chromatographed over silica gel with 7:3 hexane/ethyl acetate to provide 2-chloromethylthiophene (1.52 g, 57%) as an oil.

A suspension of sodium hydride (0.271 g, 11.3 mmol) in dry glyme (40 mL) under argon was treated dropwise with trimethyl phosphonoacetate (1.87 g, 10.3 mmol) in glyme (5 mL). The resulting mixture was stirred at room temperature for 1.5 hours. Then 2-chloromethyl-thiophene (1.5 g, 11.3 mmol) was added, and the mixture was stirred at 65°C for 18 hours. The reaction was partitioned between water and ethyl acetate, and the organic layer was washed with water and brine, dried with anhydrous magnesium sulfate and concentrated to 1.9 g of an oil. This was chromatographed over silica gel 4:1 ethylacetate/hexane to afford 800 mg (28%) of trimethyl 3-(2-thienyl)-2-phosphonopropionate.

(b) methyl (E)-3-[2-n-butyl-1-{(2-chlorophenyL)methyl}-1H-imidazol-5-yl-2-(2-thienyl)methyl-2-propenoate

To a suspension of sodium hydride (69 mg, 2.87 mmol) in glyme (5 mL) was added dropwise a solution of trimethyl 3-(2-thienyl)-2-phosphonopropionate in glyme (3 mL) under an atmosphere of argon. When the gas evolution had subsided, the mixture was heated to 50°C for 15 minutes. A solution of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde (0.53 g, 1.92 mmol) in glyme (3 mL) was added, and the mixture was stirred at 60-65°C for 5 hours. The cooled reaction was partitioned between water and ethyl acetate, and the organic layer was washed with water, dried, concentrated and flash chromatographed over silica gel to give 336 mg (41%) of methyl (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl]-1H-imidazol-5-yl[-2-(2-thienyl)methyl-2-propenoate as an oil whose NMR was entirely consistent with the trans or E form of the olefin.

(c) (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

A solution of methyl (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate (336 mg, 0.783 mmol) in ethanol (10 mL) was treated with 10% sodium hydroxide solution (4 mL), and the solution was stirred for 3 hours at 25°C. The pH was adjusted to 5 and a solid precipitated. The mixture was diluted with water, cooled and filtered to provide 309 mg of solid. A crystallization from ethyl acetate gave 195 mg (60%) of (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; mp 177-179°C.

Method B (a) methyl 3-[2-n-butyl-1-{(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-3-hydroxy-2-(2-thienyl)methylpropanoate To a solution of diisopropylamine (1.96 g, 0.0194 mol) in dry tetrahydrofuran (40 mL) held at -78°C under argon was added n-butyl lithium (7.3 mL, 0.0183 mol of 2.5 M in toluene), and the mixture was stirred for 10 minutes. Then, methyl 3-(2-thienyl)propanoate (2.83 g, 0.0166 mol) in tetrahydrofuran (2 mL) was added, and the mixture was stirred for 30 minutes at -78°C. A solution of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde (3 g, 0.0111 mol) in tetrahydrofuran (4 mL) was added, and the resulting mixture was stirred at -78°C for 30 minutes. The reaction was partitioned between saturated ammonium chloride solution and ether, the organic extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated to 6.67 g of crude product. This was flash chromatographed over 70 g of silica gel with 4:1 ethyl acetate/hexane to provide 4.03 g (81%) of methyl 3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-3-hydroxy-2-(2-thienyl)methyl-propanoate.

(b) methyl 3-acetoxy-3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)methylpropanoate

A solution of methyl 3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-3-hydroxy-2-(2-thienyl)-methylpropanoate (4.03 g, 9.02 mmol) in methylene chloride (100 mL) was treated with 4-dimethylaminopyridine (0.386g, 3.16 mmol). Then acetic anhydride (8.5 mL, 9.02 mmol) was added dropwise to the stirred mixture. The mixture was stirred for 18 hours, water (35 mL) was added, the mixture was stirred for 1 hour and then diluted with ether and saturated sodium bicarbonate solution. The ether layer was washed with brine, dried with anhydrous magnesium sulfate and evaporated to give the title 3-acetoxy derivative as an oil (4.37 g, 99%).

(c) methyl (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate

A mixture of methyl 3-acetoxy-3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)-meth-

ylpropanoate (4.36 g, 8.92 mmol) in dry toluene (80 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.2 mL, 21.4 mmol), and the resulting solution was heated at 80°C under argon for 3 hours. The solvent was evaporated, the residue triturated with ether and activated charcoal was added. After filtration, the filtrate was concentrated to 6.29 g of an oil that was chromatographed over silica gel with 65:35 hexane/ethyl acetate to give 2.89 g (76%) of methyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)-methyl]-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propenoate whose NMR and TLC (50% ethyl acetate in hexane on silica gel) were identical to the product prepared by Method A.

(d) (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

Basic hydrolysis of this ester (2.88 g, 6.71 mmol) according to Method A (iii) gave 2.59 g (93%) of (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; mp 175-177°C that was identical to the product from Method A.

Examples 2-5

[0056] In Table I are listed other examples of alkenoic acids prepared from 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde by the methods described in Example 1 (Method A). The reagents and products are shown in Table I.

Table I

Alkenoic Acids

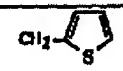
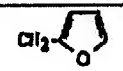
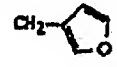
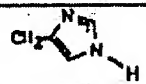
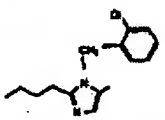
Example	Reactant[b]	R	R^1	Products (percentage yield) (E)	(Z)
1	$(MeO)_2P(O)CH(CH_2\text{-}2\text{-thienyl})\text{-}COOMe$[c]	Me H		oil mp 177-179°C (70)	- -
2	$(MeO)_2P(O)CH(CH_2\text{-}2\text{-furyl})\text{-}COOMe$[d]	Me H		oil (38) mp 180.5-182°C (73)	oil (21) mp 134.5-136°C (38)
3	$(MeO)_2P(O)CH(CH_2\text{-}3\text{-furyl})\text{-}COOMe$[d]	Me H		oil (39) mp 167.5-169°C (57)	oil (24) -

Table I

Alkenoic Acids
(Continued)

Example	Reactant[b]	R	R^1	Products (percentage yield) (Z) (a) IM, H, CO_2R, R^1	Products (percentage yield) (Z) (a) IM, H, R^1, CO_2R
4	$(MeO)_2P(O)CH(CH_2$-4-(1-tosyl) imidazole)$COOMe$[c]	Me H		oil mp 230-231°C (70)	- -
5	$(MeO)_2P(O)CH(CH_2$-3-thienyl)-$COOMe$[c]	Me H		oil (50) mp 192-193.5°C (74)	oil (38) mp 128.5-130°C (48)

a IM =  ; b Prepared as in c;
c Reactants for 2-5 prepared as in Method A(i), Example 1 except 2-chloromethylfuran, 3-chloromethylfuran, 4-acetoxymethyl-1-tosylimidazole, and 3-chloromethylthiophene are used in place of 2-chloromethylthiophene.

Example 6

(E and Z)-3-[2-n-Butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoic Acid

[0057]

Method A To a suspension of sodium hydride (0.02 mol) in glyme (30 mL) is added dropwise under argon trimethyl 3-(5-methyl-2-furyl)-2-phosphonopropionate (0.02 mol). After one hour at ambient temperature, 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde (0.0137 mol) is added, and the mixture is stirred at 40°C for one hour. The reaction is quenched with ice water, the product extracted into ether and solvent evaporated to give methyl (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate. The (E) ester is dissolved in ethanol (4 mL) and 10% sodium hydroxide solution (0.5 mL) is added. The solution is stirred at 25°C under argon for 17 hours, 10% hydrochloric acid solution is added to pH 3.5 and the solid is filtered, washed with water, and dried at 40°C in vacuum to give E-3-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoic acid.

Method B (i) 2-n-butyl-1-(trimethylsilyl)ethoxymethylimidazole

Hexane-washed 80% sodium hydride (1.45 g, 0.0483 mol) in dimethylformamide (80 mL) under argon was treated with a solution of 2-n-butylimidazole (5.45 g, 0.0439 mol) in dimethylformamide (14 mL) dropwise at 25°C and the reaction was stirred an additional hour. Then 2-(trimethylsilyl)-ethoxymethyl chloride (SEM-Cl) (7.68 g, 0.0461 mol) was added, the mixture was stirred for 18 hours at ambient temperature and then partitioned between ice water and ethyl acetate. The washed, dried, concentrated organic solution was chromatographed over silica gel with 1:1 hexane in ethyl acetate to yield 10.8 g (96%) of 2-n-butyl-1-(trimethyl-silyl)ethoxymethyl-imidazole.

(ii) 2-n-butyl-5-tributyltin-1-(trimethylsilyl)ethoxymethylimidazole

A solution of 2-n-butyl-1-SEM imidazole (prepared above) (6.37 g, 0.025 mol) in ethyl ether (125 mL) was treated dropwise with n-butyl lithium (0.0255 mol, 10.2 mL of 2.5 M in hexane) under argon at room temperature. After being stirred for an additional 45 minutes, tributyltin chloride (8.83 g, 7.4 mL, 0.026 mol) was added dropwise. The suspension was stirred overnight, saturated ammonium chloride solution was added and the ether layer was separated, washed with brine, dried over sodium sulfate, concentrated and flash chromatographed over silica gel with 3:1 hexane/ethyl acetate to provide 11.3 g (83%) of 2-n-butyl-5-tributyltin-1-(trimethylsilyl)ethoxymethylimidazole.

(iii) ethyl (E and Z)-3-[2-n-butyl-1-{(trimethylsilyl)ethoxymethyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate

To a solution of n-butyl-5-tributyltin-1-(trimethyl-silyl)ethoxymethylimidazole (0.0208 mol) in m-xylene (150 mL) is added ethyl 3-bromo-2-(5-methyl-2-furyl)methyl-2-propenoate (0.0233 mol), followed by tetrakis(triphenyl-phosphine)palladium(0) (0.416 mmol). The reaction mixture is heated at 120°C for 18 hours under argon. The cooled mixture is washed with water, 10% ammonium hydroxide solution and brine. The solution is treated with charcoal and sodium sulfate, filtered, concentrated and chromatographed over silica gel with 9:1 hexane in ethyl acetate to give ethyl (Z)-3-[2-n-butyl-1-{(trimethylsilyl)-ethoxymethyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate.

(iv) ethyl (E and Z)-3-[3-n-butyl-1-t-butoxycarbonyl-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate

A solution ethyl (E)-3-[2-n-butyl-1-{(trimethyl-silyl)ethoxymethyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate (1.24 g, 3.52 mmol) in ethanol (10 mL) is heated at 60°C for 3.5 hours with 5 N hydrochloric acid solution (20 mL). The cooled reaction is basified with 10% sodium hydroxide solution, extracted with ethyl acetate, washed with water, dried and concentrated. The residue is dissolved in methanol (15 mL), triethylamine (1.5 mL, 10.6 mmol), and di-tert-butyldicarbonate (2.3 g, 10.5 mmol) are added and the mixture is stirred for 18 hours at ambient temperature. The mixture is concentrated in vacuo and chromatographed over silica gel with 4:1 hexane/ethyl acetate to give ethyl (Z)-3-[2-n-butyl-1-t-butoxycarbonyl-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate as an oil. The (E)-isomer was prepared by the same procedure described for the (Z)-isomer.

(v) ethyl (E and Z)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate

To a stirred solution of trifluoromethanesulfonic anhydride (387 mg, 1.37 mmol) in methylene chloride (1 mL) held at -75°C under argon is added a solution of 2-chlorobenzyl alcohol (196 mg, 1.37 mmol) and diisopropylethylamine (177 mg, 1.37 mmol) in methylene chloride (4 mL). After stirring for 20 minutes at -75°C, a solution of ethyl

(Z)-3-[2-n-butyl-1-t-butoxycarbonyl-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate in methylene chloride (2 mL) is added dropwise over 10 minutes and the mixture was stirred overnight at 25°C. A solution of 5% sodium bicarbonate solution is added with stirring and the layers are separated, washed and dried. The reaction mixture is evaporated to dryness, the residue triturated with 1:1 hexane/ethyl acetate, the solid filtered off and the filtrate is concentrated and chromatographed over silica gel with 7:3 hexane/ethyl acetate to provide the title compound. The title (E)-isomer is prepared by the same procedure described for the (Z) isomer.

(vi) (Z)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoic acid

The title compounds are prepared by basic hydrolysis of the corresponding ethyl esters according to the procedure described in Example 6, Method A.

Example 7

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-butenoic Acid

[0058]

(i) 2-n-butyl-1-(2-chlorophenyl)methyl-5-(α-hydroxy)ethyl-1H-imidazole

A solution of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-carboxaldehyde (Example 1(iii)) (1.1 g, 3.97 mmol) was dissolved in dry tetrahydrofuran (15 mL), cooled to -78°C under argon and a solution of methyl lithium (3.64 ml of 1.2 M in diethyl ether, 4.57 mmol) was added dropwise. The mixture was stirred for 1.5 hours, quenched with ammonium chloride solution, warmed to ambient temperature and extracted with ethyl acetate. The washed, dried, concentrated product was flashed chromatographed over silica gel with ethyl acetate to provide 1.07 g (92%) of 2-n-butyl-1-(2-chlorophenyl)methyl-5-(a-hydroxy)ethyl-1H-imidazole.

(ii) [2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]methyl ketone

A mixture of 2-n-butyl-1-(2-chlorophenyl)methyl-5-(α-hydroxy)ethyl-1H-imidazole (1.07 g, 3.65 mmol), activated manganese dioxide (6 g) and toluene (75 mL) was heated at 90 to 100°C under a slight vacuum with a Dean Stark water separator for 17 hours. The inorganics were filtered, the concentrated filtrate was applied to a flash silica gel column and the product was eluted with 3:7 hexane/ethyl acetate to give 0.628 g (59%) of [2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]methyl ketone.

(iii) methyl (E)-3-[2-n-butyl-1-[(2-chloro-phenyl)methyl]-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-butenoate

To absolute ethanol (3 mL) is added freshly cut sodium (55 mg). Then trimethyl 3-(3-thienyl)-2-phosphono-propionate (2.16 mmol) and [2-n-butyl-1-[(2-chlorophenyl)-methyl]-1H-imidazole-5-yl]methyl ketone (0.628 g, 2.16 mmol) are added and the mixture is stirred at 70°C for 17 hours. The reaction is concentrated, partitioned between ethyl acetate and water, and the organic layer was washed with water, dried, concentrated and chromatographed to afford the title compound.

(iv) (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-butenoic acid

The title compound is prepared according to Example 1 (Method A,iii) by using methyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-butenoate in place of methyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate.

Example 8

(E)-3-[2-n-Butyl-1-[(2-chloro-6-fluoro-phenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propenoic Acid

[0059]

(i) 2-n-butyl-1-(2-chloro-6-fluorophenyl)methyl-1H-imidazole

A solution of 2-n-butylimidazole (3.75 g, 0.03 mol) in dry dimethylformamide (4 mL) was added to sodium hydride (0.95 g) in dimethylformamide (18 mL). After the gas evolution subsided, the mixture was stirred one hour under argon and 2-chloro-6-fluorobenzylchloride (5.5. g, 0.031 mol) in dimethylformamide (7 mL) was added to produce an exotherm. The mixture was stirred for 17 hours at ambient temperature, diluted with ice water and extracted with ethyl acetate. The washed, dried, concentrated organic layer provided 7.63 (94%) of the title compound whose NMR was consistent with the structure. This material was used without further purification.

(ii) 2-n-butyl-1-(2-chloro-6-fluorophenyl)-methyl-1H-imidazol-5-carboxaldehyde

The procedures of Example 1(ii-iii) were used. From 7.63 g of crude 2-n-butyl-1-(2-chloro-6-fluorophenyl)-methyl-1H-imidazole and proportional amounts of other reagents was obtained 2.8 g of 2-n-butyl-1-(2-chloro-6-fluorophenyl)methyl-5-hydroxymethyl-1H-imidazole after chromatography over silica gel with 3% of methanol in methylene chloride; mp 106-108°C (from ethyl acetate). This material was oxidized with manganese dioxide and worked up as described above to give 0.88 g (63%) of 2-n-butyl-2-(2-chloro-6-fluorophenyl)methyl-1H-imidazol-5-carboxaldehyde; mp 88-90°C (from ethyl acetate).

(iii) (E)-3-[2-n-butyl-1-[(2-chloro-6-fluorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

The procedure of Example 1, Method A is used. 2-n-Butyl-1-(2-chloro-6-fluorophenyl)-methyl-1H-imidazole-5-carboxaldehyde, trimethyl 3-(2-thienyl)-2-phosphono-propionate, sodium hydride and glyme are held at 60°C for 1 hour to give, after chromatography over silica gel with 50% of hexane in ethyl acetate, methyl (E)-[2-n-butyl-1-[(2-chloro-6-fluorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate and corresponding cis or (Z)-isomer. The (E)-isomer is hydrolyzed to afford (E)-3-[2-n-butyl-1-[(2-chloro-6-fluorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid.

Example 9

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)-2-propenoic Acid

[0060] A mixture of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde (2 mmol), 2-thienylacetic acid (2.3 mmol), potassium carbonate (0.91 mmol), and acetic anhydride (1 mL) is heated gradually to 140°C and held at this temperature for 6 hours. The cooled reaction is diluted with water and the solid is separated, triturated several times with ether, and the solid is crystallized to give the title compound.

Example 10

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-furyl)-2-propenoic Acid

[0061] This compound is prepared according to Example 9, using 2-furylacetic acid in place of 2-thienylacetic acid.

Example 11

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-heptenoic Acid

[0062]

(i) Ethyl 3-trifluoromethane-sulfonyloxy-2-heptenoate

Ethyl 3-ketoheptanoate (2.07 g, 12 mmol) was dissolved in dimethylformamide (60 mL) under argon and sodium hydride (357 mg, 14.4 mmol) was added. After 30 minutes at room temperature the solid N-phenyltrifluoromethanesulfonamide (Tetra. Letters, (1983), 24, 979) (4.97 g, 13.8 mmol) was added. The reaction was stirred for 2 hours, diluted with ether/water and the usual workup gave after chromatography with 5:95 ether/hexane 3.45 g (94%) of ethyl 3-trifluoromethanesulfonyloxy-2-heptenoate.

(ii) ethyl (E)-3-[2-n-butyl-1-[(trimethyl-silyl)ethoxymethyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-heptenoate

A solution of 2-n-butyl-5-tributyltin-1-(trimethylsilyl)ethoxymethyl imidazole (Example 6, Method B(ii)) (3.63 mmol) and ethyl 3-trifluoromethanesulfonyloxy-2-(2-thienyl)methyl-2-heptenoate (3.62 mmol) in tetrahydrofuran (5 mL) is added to a mixture of lithium chloride (11.1 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.076 mmol) in tetrahydrofuran (10 mL). The reaction is heated to reflux under argon for 5 hours, cooled, diluted with ether and the ether layer is washed with water, 10% ammonium hydroxide solution and brine. The extract is dried with sodium sulfate and concentrated. The product is chromatographed over silica gel with a gradient of hexane in ethyl acetate to give the title compound.

(iii) ethyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-heptenoate

The procedure of Example 6, Method B(iv,v) is followed using ethyl (E)-3-[2-n-butyl-1-[(trimethylsilyl)-ethoxymethyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-heptenoate in place of ethyl (E)-3-[2-n-butyl-1-[(trimethylsilyl)ethoxymethyl]-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-heptanoate to give the title compound.

(iv) (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-heptenoic acid

The ethyl ester, prepared above, is dissolved in ethanol and 10% sodium hydroxide solution is added. An additional 1 ml of base is added incrementally over several hours and the mixture is stirred overnight at room temperature. The cooled reaction was acidified to pH 5 with dilute hydrochloric acid solution, extracted with methylene chloride and the resulting residue is triturated with ether/hexane to provide the title compound.

Example 12

(E)-3-[2-n-Butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-4-(3-thienyl)-2-butenoic Acid

[0063]

(i) Ethyl 4-(3-thienyl)-3-trifluoromethanesulfonyloxy-2-butenoate

This compound was prepared according to Example 11(i) using ethyl 4-(3-thienyl)-3-ketobutanoate in place of ethyl 3-ketoheptanoate.

(ii) ethyl (E)-3-[2-n-butyl-1-{(trimethylsilyl)-ethoxymethyl}-1H-imidazol-5-yl]-4-(3-thienyl)-2-butenoate

To a solution of 2-n-butyl-1-SEM-imidazole (Example 6, Method B(i)) (5.32 mmol) in ethyl ether (16 mL) is added n-butyl lithium in hexane (6.5 mmol) at a slow rate. After an additional hour of stirring at 25°C, a solution of zinc chloride in ether (6.5 mL of 1.0 M) is added followed by tetrahydrofuran (15 mL). After an additional 75 minutes of stirring, the zinc chloride imidazole adduct solution is transferred under argon to a solution of ethyl 4-(3-thienyl)-3-trifluoromethane-sulfonyloxybutenoate (6.41 mmol) and tetrakis(triphenylphosphine)palladium(0) (317 mg) in tetrahydrofuran (30 mL). The reaction mixture is stirred at 25°C for 20 hours and worked up as in Example 12(ii) to provide ethyl (E)-3-[2-n-butyl-1-{trimethylsilyl)ethoxy-methyl}-1H-imidazol-5-yl]-4-(3-thienyl)-2-butenoate.

(iii) ethyl (E)-3-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]-4-(3-thienyl)-2-butenoate

The title compound is prepared according to the procedure of Example 6, Method B(iv, v) using ethyl (E)-3-[2-n-butyl-1-{(trimethylsilyl)ethoxymethyl}-1H-imidazol-5-yl]-4-(3-thienyl)-2-butenoate in place of ethyl (E)-3-[2-n-butyl-1-{(trimethylsilyl)ethoxymethyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate. The title compound is an oil.

(iv) (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-4-(3-thienyl)-2-butenoic acid

The above ethyl ester (520 mg) is dissolved in ethanol (5 mL) and 5 N hydrochloric acid solution (40 mL), and the solution is slowly heated at 100°C with evaporation of the alcohol. After being heated at 100°C for 6 hours, the reaction is cooled and the white precipitate is collected, air-dried, and then triturated with ether/methanol to afford (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-4-(3-thienyl)-2-butenoic acid hydrochloride.

Example 13

(E)-4-[2-n-Butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]-3-(5-methyl-2-furyl)methyl-3-butenoic Acid

[0064]

(i) (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenol

A solution of methyl (E)-3-[2-n-butyl-1-{(2-chloro-phenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenoate (Example 6, Method A) (1.5 mmol) in dry tetrahydrofuran (10 mL) held at -78°C under argon is treated dropwise with a solution of diisobutyl aluminum hydride in toluene (3.30 mmol, 2.2 mL of 1.5 M). The mixture is allowed to warm to ambient temperature and stirred an additional 17 hours. Excess reducing agent is quenched with methanol and water, dilute acetic acid and methylene chloride are added, and the organic layer is washed with sodium bicarbonate solution, dried and concentrated to give the title compound.

(ii) ethyl (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenyl carbonate

To a solution of (E)-3-[2-n-butyl-1-{(2-chloro-phenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)-methyl-2-propenol (6.86 mmol) in methylene chloride (20 mL) and triethylamine (12.4 mmol) cooled to 0°C under argon is added dropwise ethyl chloroformate (1.34 g, 1.18 ml, 12 mmol). The reaction is then stirred at ambient temperature overnight. Ethyl acetate is added, the precipitate filtered and the concentrated filtrate is flash chromatographed over silica gel with 3:7 hexane/ethyl acetate to provide the title compound.

(iii) ethyl (E)-4-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazole-5-yl]-3-(5-methyl-2-furyl)methyl-3-butenoate

A solution of ethyl (E)-3-[2-n-butyl-1-{(2-chloro-phenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-furyl)methyl-2-propenyl carbonate (3.77 mmol) in tetrahydrofuran (12 mL) under an atmosphere of carbon monoxide is treated with triphenylphosphine (0.188 mmol) and palladium diacetate and the mixture is heated at 40°C for 2-1/2 hours. The concentrated reaction mixture is applied to a flash column of silica gel and eluted with 1:1 hexane/ethyl acetate to afford the title compound.

(iv) (E)-4-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]/-3-(5-methyl-2-furyl)methyl-3-butenoic acid

The compound is prepared according to the procedure of Example 1, Method A(iii) using the above prepared ethyl ester in place of ethyl (E)-3-[2-n-butyl-1-{(2-chloro-phenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate.

Example 14

(E)-4-[2-n-Butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-methyl- and -2,2-dimethyl-3-(2-thienyl)methyl-3-butenoic Acid

[0065]

(i) ethyl (E)-4-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-methyl-3-(2-thienyl)methyl-3-butenoate

Lithium diisopropylamide (0.85 mmol, 1 M in tetrahydrofuran) is cooled to -78° under argon and a solution of ethyl (E)-4-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]-3-(2-thienyl)methyl)-3-butenoate (0.709 mmol), prepared as in Example 13 using methyl (E) 3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate (Example 1), in tetrahydrofuran (5 mL) is added. After 10 minutes methyl iodide (0.71 mmol) is added. The mixture is then stirred at room temperature overnight, diluted with 10% ammonium chloride and extracted with ethyl acetate. The dried, concentrated product is chromatographed over silica gel with 6:4 hexane/ethyl acetate to give the title compound.

(ii) (E)-4-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-methyl-3-(2-thienyl)methyl-3-butenoic acid

A solution of the above prepared ethyl ester in ethanol is heated to reflux with 10% sodium hydroxide solution for 2 hours. The ethanol is evaporated, water is added and the aqueous layer is extracted with ether. The water layer is acidified to pH 1 with dilute hydrochloric acid solution, extracted with ethyl acetate, dried and concentrated to a solid. Trituration with ether provides the hydrochloride salt of the title compound.

(iii) (E)-4-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2,2-dimethyl-3-(2-thienyl)methyl-3-butenoic acid

This compound is prepared according to the procedure of Example 14(i,ii) using two equivalents of methyl iodide.

Example 15

(E)-4-[2-n-Butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-3-(2-thienyl)methyl-3-butenoic Acid

[0066] This compound is prepared according to the procedure of Example 14(i,ii) using less than one equivalent of 2-chloromethylthiophene in place of methyl iodide.

Example 16

(E)-4-[2-n-Butyl-1-{2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-benzyl-3-(2-thienyl)methyl-3-butenoic Acid

[0067] This compound is prepared according to Example 14(i,ii) but using less than one equivalent of benzyl bromide at higher solvent dilution.

Example 17

(E,E)-5-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-4-(2-thienyl)methyl-2,4-pentadienoic Acid

[0068]

(i) (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl)-2-(2-thienyl)methyl-2-propenol

To a solution of methyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl)-2-(2-thienyl)methyl-2-propenoate, prepared in Example 1, ((2.60 g. 6.06 mmol) in 35 mL of tetrahydrofuran at -78°C under argon was added a solution of diisobutylaluminum hydride (1.5 M, 8.9 mL, 13.3 mmol). After the addition was complete, the reaction mixture was allowed to warm to room temperature, with stirring being continued for one hour. The reaction was worked up by the slow addition of methanol, followed by the addition of glacial acetic acid, then four drops of 10% aqueous hydrochloric acid solution. Water (10 mL) was added and the reaction mixture was stirred at room temperature overnight. The product was extracted with ethyl acetate (3x75 mL) after 40 mL of water had been added to the mixture. The combined extracts were dried with anhydrous magnesium sulfate and the solvents were removed in vacuo. The residue was triturated with diethyl ether. The resulting solid was filtered to give 1.72 g (71%) of product; mp 114-115°C.

(ii) (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propionaldehyde

To a suspension of 8.0 g of manganese dioxide in 80 mL of benzene was added (E)-3-[2-n-butyl-1-[(2-chlorophenyl)-methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenol (1.61 g, 4.02 mmol). The reaction was stirred vigorously for 0.5 hours. The solids were filtered and washed with ethyl acetate. The filtrate was concentrated to near-dryness and then the residue was triturated with hexane. The resulting solid was filtered to give 0.669 g of product; mp 163.5-164.6°C.

The filter cake was heated with ethyl acetate for 10 minutes and the solids were filtered. The filtrate was cooled in ice/water and the resulting solid was filtered to give 0.712 g of additional product; mp 163.5-164.5°C.

(iii) ethyl (E,E)5-[2-n-butyl-1-[(2-chlorophenyl)-methyl)-1H-imidazol-5-yl]-4-(2-thienyl)-methyl-2,4-pentadienoate

To a suspension of (E)-3-[2-n-butyl-1-[(2-chloro-phenyl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propionaldehyde in 8 mL of toluene was added (carbethoxy-methyl)triphenylphosphorane. The reaction was heated overnight at 40°C. After cooling to room temperature, the solids were filtered to give 0.181 mg of crude product. Chromatography on silica gel eluting with hexane/ethyl acetate (6:4) gave 0.2345 g (50%) of the title compound as an oil.

(iv) (E,E)-5-[2-n-butyl-1-[(2-chlorophenyl)-methyl]-1H-imidazol-5-yl]-4-(2-thienyl)-methyl-2,4-pentadienoic acid

The title compound was prepared according to the procedure of Example 1 (iv), Method A(c) using the above prepared ethyl ester; hydrochloric acid salt, mp 191-192.5°C.

Alternately, the sodium salt of the acid is isolated directly from the reaction mixture, prior to neutralization. The crude basic reaction solution is applied to a reverse-phase flash column equilibrated with water. The inorganics are washed from the column with water (3 void volumes) and then the product is eluted with a 50:50 mixture of acetonitrile in water. The acetonitrile is removed in vacuo and then the desired sodium salt is obtained after lyophilization.

Example 18

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, 2-(N,N-Diethylamino-2-oxoethyl Ester

[0069] A solution of (E)-3-[2-n-butyl-1-[(2-chlorophenyl)-methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid (Example 1) (5 mmol) in dry dimethylforma-mide (10 mL) was treated with 2-chloro-N,N-diethyl-acetamide (5.51 mmol) followed by powdered potassium carbonate. This mixture was heated at 70°C for 7 hours, diluted with water and extracted with ethyl acetate. The water-washed, dried, concentrated product solidifies and after trituration with ether/hexane affords the title ester; mp 139-140°C.

Example 19

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl-4-hydroxymethyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0070]

(i) 2-n-butyl-1-(2-chlorophenyl)methyl-4-(t-butyl-dimethylsilyloxy)-methyl-1H-imidazol-5-carboxaldehyde

A solution of 2-n-butyl-1-(2-chlorophenyl)methyl-4,5-bis(hydroxy)methyl-1H-imidazole (Example 1(ii)) (310 mg, 1 mmol) in methylene chloride (5 mL) was treated with 4-dimethylaminopyridine (5.2 mg), triethylamine (1.5 mmol) and t-butyl dimethylsilyl chloride (192 mg, 1.24 mmol). The mixture was stirred at 25°C for 20 hours, diluted with water and the organic layer was washed well with water, dried, concentrated and chromatographed over silica gel with an ethyl acetate/methanol gradient to afford 127 mg (24%) of the bis (4,5-t-butyldimethylsilyl) ether and 252 mg (59%) of 2-n-butyl-1-(2-chlorophenyl)methyl-4-t-butyldimethy-silyloxymethyl-5-hydroxymethyl-1H-imidazole. This monoether (252 mg) was oxidized to the 5-carboxaldehyde using manganese dioxide as described in Example 1(iii) to provide 170 mg of 2-n-butyl-1-(2-chlorophenyl)-methyl-4-(t-butyldimethylsilyloxy)methyl-1H-imidazol-5-carboxaldehyde as an oil.

(ii) ethyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-4-(t-butyldimethyl-silyloxy)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate

In tetrahydrofuran (80 mL) is added n-butyl lithium (15.5 mmol in hexane) and at -78°C under argon is then added diisopropylamine (2.4 mL, 17.1 mmol). Methyl 3-(2-thienyl)propanoate (15.3 mmol) is added neat over 5-6 minutes, and the mixture was stirred an additional 30 minutes at -78°C. A solution of 2-n-butyl-1-(2-chloro-phenyl-methyl-4-(t-butyldimethylsilyloxy)methyl-1H-imidazol-5-carboxaldehyde (10.2 mmol) in tetrahydrofuran (10 mL) is added via cannula, and the reaction mixture is stirred for 15 minutes. The reaction is partitioned between saturated ammonium chloride and ether, and the ether layer is washed with water, dried and concentrated to give crude product. This is chromatographed over silica gel with 20-50% of ethyl acetate in hexane to afford a mixture of isomeric β-hydroxyester products. A solution of this mixture (8.54 mmol) in methylene chloride (100 mL) is treated with 4-dimethylaminopyridine (3 mmol) followed by acetic anhydride (84 mmol), and the solution is stirred at room temperature for 5 hours. The reaction is poured into water, stirred for 20 minutes and the product is extracted into ether. The ether extracts are washed with dilute hydrochloric acid solution, water, sodium bicarbonate solution and brine. The dried, concentrated mixture of β-acetoxyester products is used directly in the elimination reaction. To a solution of the β-acetoxyester product (4.5 mmol) in toluene (60 mL) is added of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (10.9 mmol), and the mixture is heated at 90°C for 24 hours. The reaction is concentrated to 10 mL, diluted with ether and flash filtered through a 14 x 3 cm plug of silica gel with ether rinses to afford the crude olefinic product. Chromatography over silica gel with an ethyl acetate in hexane gradient gives homogeneous ethyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-4-t-butyldimethyl-silyloxymethyl)-1H-imidazol-5-yl)-2-(2-thienyl)methyl-2-propenoate. The elimination of the acetate with DBU produces predominantly the trans (E) isomer.

(iii) (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl-4-hydroxymethyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

A solution of ethyl (E)-3-[2-n-butyl-1-[(2-chloro-phenyl)-4-t-butyldimethylsilyloxymethyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate (0.287 mmol) in absolute ethanol (3 mL) is treated portionwise at 6 hour intervals with 10% sodium hydroxide solution (3 x 1 mL). After being stirred overnight at 25°C, the reaction is heated to 50°C for 4 hours, then concentrated in vacuo. The residual product is taken up in water, acidified to pH 5-6 and extracted with methylene chloride. The isolated, dried, concentrated product is triturated with methanol/ether to provide the title compound.

Example 20

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic Acid

[0071]

(i) methyl 3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-3-hydroxy-2-(4-pyridyl)methylpropanoate

To a solution of diisopropylamine (3.58 mL, 25.6 mmol) in dry tetrahydrofuran (50 mL) held at -78°C under argon was added n-butyl lithium (10.2 mL, 25.6 mmol of 2.5 M in toluene), and the mixture was stirred for 10 minutes. Then, methyl 3-(4-pyridyl)propanoate (4.22 g, 25.6 mmol) (prepared by reaction of 4-pyridine carboxaldehyde with trimethyl phosphonoacetate in the presence of sodium hydride in ethylene glycol dimethyl ether, followed by

catalytic hydrogenation of the double bond with 10% palladium on carbon at 3 atmosphere of hydrogen in an ethyl acetate solution (98%) to provide the saturated ester) was added in tetrahydrofuran (40 mL) and this mixture was stirred for 30 minutes at -78°C. A solution of 2-n-butyl-1-(2-chloro-phenyl)methyl-1H-imidazol-5-carboxaldehyde (5.9 g, 21.3 mmol) in tetrahydrofuran (10 mL) was added and stirring was continued for 30 minutes at -78°C. The reaction was partitioned between saturated ammonium chloride solution and ether, the organic extract was washed with brine, dried over magnesium sulfate, concentrated and flash chromatographed over silica gel with 5% methanol in ethyl acetate to provide 3.32 g (30%) of methyl 3-[2-n-butyl-1-(2-chlorophenyl)-methyl-1H-imidazol-5-yl]-3-hydroxy-2-(4-pyridyl)methyl-propanoate. TLC on silica gel with 5% methanol in ethyl acetate showed a homogenous product with an R_f of 0.79.

(ii) methyl 3-acetoxy-3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(4-pyridyl)propanoate

A solution of methyl 3-[2-n-butyl-1-(2-chlorophenyl)-methyl-1H-imidazol-5-yl]-3-hydroxy-2-(4-pyridyl)-methyl-propanoate (3.32 g, 7.5 mmol) methylene chloride (50 mL), 4-dimethylaminopyridine (150 mg, 1.3 mmol) and acetic anhydride (7.1 mL, 75 mmol) was stirred at ambient temperature for 18 hours. Water (5 mL) was added, the mixture was stirred for 2 hours and then diluted with methylene chloride and 5% sodium bicarbonate solution. The organic phase was washed with 5% sodium bicarbonate solution and brine, dried and concentrated to give 4 g of the crude title compound. TLC on silica gel with 5% methanol ethyl acetate showed essentially one spot material with an R_f of 0.86. No starting material was detected. This material was not purified further.

(iii) methyl (E)-3-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoate

A mixture of methyl 3-acetoxy-3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(4-pyridyl)-propenoate (7.5 mmol), toluene (50 mL) and 1,8-diaza-bicyclo[5,4,0]-undec-7-ene (DBU) (3.4 mL, 22.5 mmol) was heated at 90°C for 18 hours under argon. The cooled mixture was diluted with ether, and washed with brine, dried and concentrated to 3.1 g (97%) of the title compound. NMR showed that the trans or E isomer was the primary product.

(iv) (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(4-pyridyl)-methyl-2-propenoic acid

A solution of methyl (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoate (3.1 g, 7.3 mmol) in ethanol (16 mL) was treated with 10% sodium hydroxide solution and the mixture was stirred for 18 hours at 25°C. The solution was concentrated in vacuum, water was added, the pH was adjusted to 6.5 and the resulting solid was filtered, washed with water and crystallized from methanol/ether to afford 0.48 g of (E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic acid; mp 178-182°C (d).

Examples 21-26

[0072] In Table II are listed other examples of alkenoic acids prepared by the methods described in Example 20 (i-iv). The starting materials and products are shown in Table II.

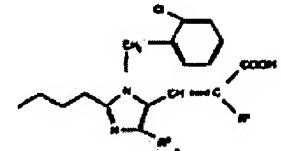
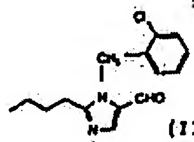
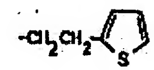
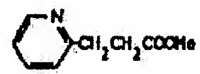
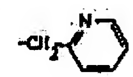
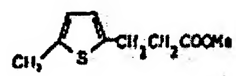
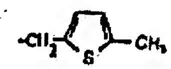
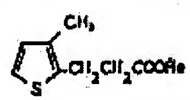
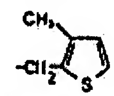
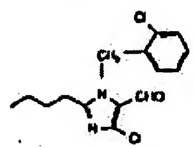
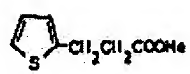
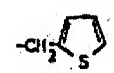


Table II

Example	Starting Materials		R^3	Product $(R^5)^a$	mp
21	 (II)		H		184-185°C
22	(II)		H		156-160°C (d)
23	(II)		H		161-164°C
24	(II)		H		169-170°C
25	(II)		H		173.5-175°C[b]
26			Cl		175-176°C[b]

[a] Product prepared by the 4 step synthetic route described in Example 20. The penultimate olefinic ester is purified, if necessary, by chromatography over silica gel with ethyl acetate/hexanes or methanol/ethyl acetate mixtures.

[b] Hydrochloride salt.

Example 27

[0073] By the procedure of Example 20 (i-iv) using in place of methyl 3-(4-pyridyl)propanoate, the following:

methyl 3-(4-thiazolyl)propanoate,
methyl 3-(1,2,3,4-tetrazol-5-yl)propanoate, and
methyl 3-(1-tosylpyrazol-3-yl)propanoate; the products are:
3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-thiazolyl)methyL-2-propenoic acid,
3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(1,2,3,4-tetrazol-5-yl)methyl-2-propenoic acid, and
3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(3-pyrazolyl)methyl-2-propenoic acid.

Example 28

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-fluoro-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0074] Anhydrous hydrochloric acid (20.5 g, 0.562 mol) bubbled into a stirred solution of valeronitrile (31.8 g, 40.0 mL, 0.383 mol) in methanol (13.47 g, 17 mL, 0.421 mol) which was cooled by a ice/acetone bath. The reaction was capped tightly and then stored at 10°C overnight. To this solid mixture at 10°C under argon was added 100 mL of t-butyl methyl ether. Once a free-flowing crystalline mixture had formed, the solid was collected and washed with 400 mL of t-butyl methyl ether. The solid was immediately placed in a vacuum desiccator over phosphoric anhydride and sodium hydroxide to give 55.50 g (96%) of valeramidine methyl ether hydrochloride; mp 103-105°C.

[0075] The procedure of W. Lwowski, Synthesis, 263 (1971) was followed. To a mixture of valeramidine methyl ether hydrochloride (37.91 g, 0.25 mol) and 50% aqueous cyanamide (13.53 g, 25 mL, 0.322 mol) cooled in an ice bath was added portionwise anhydrous disodium phosphate (12.01 g, 0.0846 mol). After the addition was complete, the ice bath was removed and an oil and solid began to come out of solution. After stirring for an additional 30 minutes, the oil was decanted from the solid. The solid was partitioned between water and diethyl ether and the oil was also dissolved in diethyl ether. The combined organic extracts were washed with saturated sodium chloride solution and then dried with anhydrous sodium sulfate. The solvent was removed in vacuo to give 33.06 g (94%) of valercyanamidine methyl ether.

[0076] To a solution of the amidine methyl ether prepared above (33.06 g, 0.236 mol) in 225 mL of absolute ethanol was added in one portion 2-chlorobenzylamine (33.39 g, 0.236 mol). The reaction was stirred at room temperature for 2 hours and then the solvent was removed in vacuo to give 55.4 g (94%) of a solid, whose NMR indicated the absence of the methyl ether functionality.

[0077] The secondary amine was alkylated using the following procedure. A mixture of the product prepared above (35.0 g, 0.14 mol) and potassium carbonate (67.72 g, 0.49 mol) in 200 mL of dimethylformamide was stirred under argon at 60°C for 15 minutes. To this mixture was added over 10 minutes ethyl bromoacetate (24.56 g, 0.143 mol). After the addition was complete, the reaction temperature was raised to 75-80°C. After 30 minutes, the reaction mixture was filtered. The filtrate was concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic extract was washed with water (5x) and saturated sodium chloride solution. The organic extract was dried with anhydrous sodium sulfate and then the solvent was removed in vacuo. The crude product was chromatographed on silica gel eluting with ethyl acetate in hexane to give 37.15 g (79%) of an oil.

[0078] 2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-amino-5-carboethoxyimidazole was prepared by the following procedure. Sodium metal (2.54 g, 0.110 g-atom) was dissolved in absolute ethanol under argon. To this solution was added a solution of the above-prepared product (37.07 g, 0.110 mol) in 175 mL of absolute ethanol over a 15 minute period. After the addition was complete the reaction mixture was stirred for one hour at room temperature. The resulting solid was collected, washed with water, and air-dried to give 25 g of product; mp 120-121°C.

[0079] The 4-amino product was fluorinated using the procedure of K.L. Kirk and L.J. Cohen, JACS, 95 (14), 4619 (1973). Fluoroboric acid (48%, 150 mL) was added to 2-n-butyl-1-[(2-chlorophenyl)methyl]-4-amino-5-carboethoxyimidazole (10.75 g, 0.032 mol) in a quartz flask. The resulting solid mass was sonicated and stirred vigorously to form a suspension. This suspension was cooled to 0°C and then sodium nitrite (2.80 g, 0.0406 mol) in 5 mL of water was added slowly. The ice bath was removed and then the reaction mixture was irradiated for 20 hours with a 450-watt mercury vapor lamp placed in a quartz immersion well, cooled by circulating water. The reaction mixture was cooled to -20°C and the pH was adjusted to 6.4 with 50% aqueous sodium hydroxide. The product was extracted into ethyl acetate (3x) and the combined extracts were washed with water and saturated sodium chloride solution. The organic extract was dried with anhydrous sodium sulfate and concentrated to give 8.43 g of a crude product, which was chromatographed on silica gel eluting with chloroform to give 4.31 g of 2-n-butyl-1-[(2-chlorophenyl)methyl]-4-fluoro-5-carboethoxyimidazole.

[0080] This carboethoxy compound was converted to the corresponding 5-formyl derivative following the procedure of Example 17 (i and ii).

[0081] 2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-fluoro-5-formylimidazole was converted to E-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-4-fluoro-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid following the procedure of Example 20 (i-iv) replacing methyl 3-(4-pyridyl)propanoate with methyl 3-(2-thienyl)-propanoate; mp 126-127°C.

Example 29

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-bromo-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0082] By the procedure of Example 28 using the corresponding 4-bromo starting material (prepared by the method described in U.S. Patent No. 4,340,598), the title compound is prepared.

Example 30

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-trifluoromethyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0083] Using 2-n-butyl-1-(2-chlorophenyl)methyl-4-trifluoroethyl-1H-imidazol-5-carboxaldehyde (prepared by treating the corresponding 4-bromo compound with trifluoromethyl iodide and copper) in the procedure of Example 20 gives the title compound.

Example 31

[0084] By the procedure of Example 1, using in place of 2-chlorobenzyl bromide, the following:

2-methylbenzyl bromide,
4-methoxybenzyl bromide, and
4-phenylbenzyl bromide;
and using the phosphonopropionate of Example 1, $(MeO)_2P(O)CH(CH_2$-2-thienyl$)COOMe$, the following products are obtained:
(E)-3-[2-n-butyl-1-[(2-methylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
(E)-3-[2-n-butyl-1-[(4-methoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, and
(E)-3-[2-n-butyl-1-[(4-phenylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid.

Example 32

[0085] The following methyl ester of a propenoate are prepared as in Example 31:

methyl (E)-3-[2-n-butyl-1-[(4-methoxyphenyl)-methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate.
This is treated with boron tribromide in methylene chloride at room temperature for six hours and then the reaction mixture is condensed and treated with a mixture of ethyl acetate and water. The washed ethyl acetate layer gives on evaporation:
(E)-3-[2-n-butyl-1-[(4-hydroxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid.

Example 33

(E)-3-[2-(1-Butenyl)-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0086] A mixture of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde and N-bromosuccinimide in carbon tetrachloride was irradiated to give the 2-(1-bromo-butyl)imidazole which was dehydrobrominated by treating 1,8-diazabicyclo[4.5.0]undec-1-ene in tetrahydrofuran to give 2-(1-butenyl)-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde.
[0087] The above prepared intermediate and the 3-(2-thienyl)propenoate of Example 1 in the procedure of Example 1 was used to give the title compound; mp 224-226°C.

Example 34

(E)-3-[2-Phenyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0088] By the procedure of Example 1(ii) Method 2, using benzamidine methyl ether in place of valeramidine methyl ether, 2-phenyl-5-hydroxymethylimidazole is prepared and converted to 2-phenyl-1-(2-chlorophenyl)methyl-5-hydroxymethyl-1H-imidazole. The 5-hydroxymethyl group is oxidized using manganese dioxide by the procedure of Example 1 (ii). The resulting 2-phenyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde is used in the procedure of Example 21 with methyl 3-(2-thienyl)propanoate to give the title compound.

Example 35

[0089] By the procedure of Example 34 using the following amidine methyl ethers:

$C_{10}H_{21}C=NH(OCH_3)$ and
$C_2H_5C=NH(OCH_3)$;
the following products are obtained:
(E)-3-[2-decyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid and
(E)-3-[2-ethyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid.

Example 36

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-formyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0090] The title compound is prepared by dilute hydrochloric acid hydrolysis of the 4-t-butyldimethylsilyloxy group of ethyl 3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-4-(t-butyldimethyl-silyloxy)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate, prepared as in Example 20(ii), followed by manganese dioxide oxidation of the 4-hydroxymethyl group to the carboxaldehyde.

Example 37

3-[1-(2-Adamantyl)ethyl]-2-n-butyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0091] A mixture of 2-(1-adamantyl)ethanol (10.7 g and diisopropylethylamine (11 ml) in methylene chloride (70 ml) was added to triflic anhydride (16.75 g) in methylene chloride (70 ml) at -78°C under argon. After stirring the mixture at -78°C for 45 minutes, 1-acetyl-2-n-butyl-5-(acetoxymethyl)imidazole in methylene chloride (50 ml) was added and the mixture was allowed to stand at room temperature for 4 days, then concentrated and heated on a steam bath with 10% sodium hydroxide (250 ml), diluted with 300 ml of water, extracted with methylene chloride, dried, filtered and concentrated to give an oil. Chromatography (silica gel) in methanol-chloroform gives 5-acetoxymethyl-1-[2-(1-adamantyl)ethyl]-2-n-butylimidazole.

[0092] The above prepared compound (5.4 g) was stirred at room temperature with potassium hydroxide (5.2 g) in ethanol (200 ml) for one hour. The mixture was concentrated, poured into water, stirred and filtered to give 1-[2-(1-adamantyl)ethyl]-2-n-butyl-5-hydroxymethyl-imidazole. The hydroxymethyl group was oxidized by refluxing the imidazole compound (51.1 g) with manganese dioxide (20.3 g) in toluene (200 ml) to give 1-[2-(1-adamantyl)ethyl]-2-n-butyl-imidazol-5-carboxaldehyde.

[0093] Diisopropylamine (0.563 g) was covered with 5 ml of tetrahydrofuran and 2 ml of 2.5 M n-butyl lithium in hexane was added at -78°C. The mixture was stirred for 15 minutes, then methyl 3-(2-thienyl)propenoate (0.89 g) in 3 ml of tetrahydrofuran was added. After 20 minutes, 1.04 g of 1-[2-(1-adamantyl)ethyl]-2-n-butyl-imidazol-5-carbox-aldehyde in 3 ml of tetrahydrofuran was added and the mixture was stirred for 30 minutes at -78°C. The mixture was poured into 40 ml of saturated ammonium chloride in water, extracted with ether, dried over magnesium sulfate, filtered, concentrated and chromatographed on silica gel eluting with 70% ethyl acetate and 30% hexane to give methyl 3-[1-(2-(1-adamantyl)ethyl)-2-n-butyl-1H-imidazol-5-yl]-3-hydroxy-2-(2-thienylmethyl)propanoate. To 1.27 g of this compound in methylene chloride (25 ml) was added 4-dimethylaminopyridine (1.25 g), then acetic anhydride (2.75 g) was added dropwise. The mixture was stirred for one hour, then poured into water and worked up to give 3-acetoxy-3-[1-(2-(1-adamantyl)ethyl)-2-n-butyl-1H-imidazol-5-yl]-2-(2-thienylmethyl)propanoate.

[0094] The above prepared compound (1.2 g) was heated with 1,8-diazabicyclo[5,4,0]undec-7-ene (1 ml) in toluene (20 ml) at 80°C with stirring for one hour. The mixture was concentrated, then stirred with ether. The ether layer was decanted and dried, filtered, concentrated and chromatographed to give methyl 3-[1-(2-(1-adamantyl)ethyl)-2-n-butyl-1H-imidazol-5-yl]-2-(2-thienylmethyl)-2-propenoate.

[0095] This ester (0.63 g) was hydrolyzed in ethanol (10 ml) using potassium hydroxide (0.18 g) to give the title compound; 218-220°C.

Example 38

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-carboxy-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0096] (E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-hydroxymethyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared as in Example 19, is esterified with 4-methoxy-benzyl alcohol to give the p-methoxybenzyl pro-

penoate. The 4-hydroxymethyl group in acetone is oxidized using an acidic aqueous solution containing chromic acid (Jones' reagent) and the ester is hydrolyzed using 10% sodium hydroxide to give the title compound.

Example 39

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-carbamoyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0097] 4-Methoxybenzyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-4-carboxy-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate, prepared as in Example 38, is treated with oxalyl chloride in methylene chloride at 0°C to give the acid halide which is treated with ammonium hydroxide and the ester is hydrolyzed to give the title compound.

Example 40

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-4-dimethylcarbamoyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0098] Treating the 4-chloroformyl imidazole, prepared as in Example 39, with dimethylamine instead of ammonium hydroxide gives the title compound.

Example 41

(E)-3-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl)-2-(2-thienyl)methyl-2-propenoic Acid

[0099]

(i) By the procedure of Example 1 [(ii) Method 2, (iii) and (iv) Method B] using 4-carbomethoxybenzyl alcohol in place of 2-chlorobenzyl alcohol, the title compound was prepared; mp 250-253°C.

Example 42

(E)-3-[2-n-Butyl-1-[(4-carboxy-2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0100] A suspension of 2-butylimidazol-5-aldehyde (16.92 g, 0.111 mol, prepared by manganese dioxide oxidation of the alcohol, prepared in Example 1, Method 2), chloromethyl pivalate (21.77 g, 0.145 mol), and potassium carbonate (20.07 g, 0.145 mol) in 200 ml of dimethylformamide was stirred at ambient temperature under argon for four days. The solids were removed by filtration and washed with ether. The combined filtrates were partitioned between diethyl ether and water. The ether phase was washed successively with water and brine, dried over magnesium sulfate and concentrated under vacuum to give 23.6 g of 2-n-butyl-1-pivalyloxymethylimidazole-5-aldehyde.

[0101] A mixture of ethyl 4-bromomethyl-3-chlorobenzoate (5.28 g, 0.020 mol, U.S. Patent No. 4,837,333) and 2-n-butyl-1-pivaloyloxymethyl-imidazole-5-aldehyde (4.45 g, 0.0167 mol) was heated at 100°C under argon for 18 hours. Repeated trituration with ether gave 6.38 g of a crystalline salt. A suspension of this salt in 100 ml of ethyl acetate was stirred for 0.5 hours with 100 ml of 5% aqueous sodium carbonate. The layers were separated, the aqueous layer washed with ethyl acetate, and the combined organic layers washed with water, dried over magnesium sulfate and concentrated to give an oil. Chromatography of this oil over silica eluting gel with ethyl acetate/hexane (1:1) gave 1.02 g of 2-n-butyl-1-[(4-carboethoxy-2-chlorophenyl)-methyl]imidazole-5-aldehyde.

[0102] Ethyl 2-carboxy-3-(2-thienyl)propionate (14 g, 0.061 mol) was prepared by stirring a solution of diethyl 2-thienylmalonate (16.8 g, 0.0655 mol) and potassium hydroxide (4.41 g, 0.0786 mol) in 200 ml of ethanol under argon at room temperature for 12 days and then purifying by removing the solvent under vacuum, dissolving the reside in water, washing the aqueous layer with aqueous hydrochloric acid and with diethyl ether.

[0103] A solution of this half-acid, half-ester (1.05 g, 4.62 mmol) in 5 ml of toluene was added to a refluxing solution of 2-n-butyl-1-[(4-carboethoxy-2-chlorophenyl)methyl]-imidazole-5-aldehyde (1.03g, 3.08 mmol) and piperidine (0.26 g, 3.08 mmol) in 60 ml of toluene. Twice, at 1 hour intervals, an additional 1 g of the half-acid, half-ester was added, and the solution was then refluxed for 17 hours. Evaporation of the toluene and chromatography of the residue over silica gel using 2:3 ethyl acetate-hexane for elution gave 0.39 g of the diester of the title product. This was hydrolyzed in 2:1 ethanol-water with 5 equivalents of potassium hydroxide for 18 hours and worked up in the usual manner to give 0.260 g of final product; mp 234-236°C. The NMR of this product was in accord with its structure.

Example 43

(E)-3-[2-n-Butyl-1-[(4-sulfonamidophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0104] The procedure of Example 42 is followed using 4-bromomethylbenzenesulfonamide (Braselton, et al., Anal. Chem., 48, 1386 (1976)) in place of methyl 4-bromomethyl-3-chlorobenzoate to give the title compound.

Example 44

(E)-3-[2-n-Butyl-1-[(4-carboxy-2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0105] The procedure of Example 42 was followed using methyl 4-bromomethyl-3-nitrobenzoate (prepared from 4-methyl-3-nitrobenzoic acid by esterification with gaseous hydrochloric acid-methanol followed by methyl bromination with N-bromosuccinimide) to give the title compound.

Example 45

(E)-3-[2-n-Butyl-1-[(4-carboxy-3-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0106] The procedure of Example 42 was followed using ethyl 4-bromomethyl-2-chlorobenzoate (U.S. Patent No. 4,837,333) in place of ethyl 4-bromomethyl-3-chlorobenzoate to give the title compound; 245-246°C.

Example 46

(E)-3-[1-[(2-Chlorophenyl)methyl]-2-propylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0107]

(i) 5-carboxymethyl-1-(2-chlorophenyl)methyl-2-thio-1H-imidazole

A solution of 2-chlorobenzylamine (14.2 g, 0.1 mol) and triethylamine (13.9 ml, 0.1 mol), in dimethylformamide (100 ml) was treated with methyl chloroacetate (10.9 g, 0.1 mol), and the mixture was heated at 50°C for 3.5 hours. The cooled reaction mixture was diluted with ether, the solids filtered and the concentrated filtrate was flash chromatographed over silica gel with 6:5 hexane in ethyl acetate to provide 15.3 g (71%) of homogeneous methyl 2-[N-(2-chlorophenyl)methyl]aminoacetate. This product (15.2 g, 0.071 mol) in mixed xylenes (100 ml) was treated with 98% formic acid (2.74 ml), 0.0711 mol) and the mixture was refluxed from 2.5 hours with a Dean-Stark water separator. Evaporation gave 17.1 g (99%) of methyl 2-[N-(2-chlorophenyl)methyl-N-formyl)aminoacetate. This formylated product (17.0 g, 0.071 mol) was dissolved in methyl formate (13.3 ml, 0.216 mol) and added dropwise to a sodium methoxide mixture prepared by adding sodium metal (1.79 g, 0.0778 g-atom) to tetrahydrofuran (325 ml) followed by slow addition of methanol (3.15 ml, 0.0778 mol). The combined mixture was stirred at room temperature for 18 hours, then evaporated to dryness. This crude product was dissolved in 50% aqueous methanol (200 ml), treated with charcoal, filtered and the solution was cooled in ice. Concentrated hydrochloric acid followed by a solution of potassium thiocyanate (8.6 g, 0.0885 mol) in water (20 ml). The mixture was heated in an oil bath held at 90°C for 2.5 hours, then cooled to 10°C. The precipitated solid was filtered, washed with cold ethanol-water and dried at 60°C to provide 14.7 g (74%) of 5-carboxymethyl-1-(2-chloro-phenyl)methyl-2-thio-1H-imidazole; mp 72-74°C.

(ii) 1-(2-chlorophenyl)methyl-5-carboxymethyl-2-propylthio-1H-imidazole

A mixture of 5-carboxymethyl-1-(2-chlorophenyl)methyl-2-thio-1H-imidazole (2 g, 7.08 mmol, ethyl acetate (20 ml), 5% sodium carbonate solution (40 ml) and propyl bromide (4 ml, 44 mmol) was heated at 60°C for 18 hours. The organic layer was separated, dried over magnesium sulfate and concentrated to 2.23 g of crude product. Trituration with ether provided 1.63 g (71%) of 5-carboxymethyl-1-(2-chlorophenyl)methyl-2-propylthio-1H-imidazole; mp 68-71°C (from hexane).

(iii) E-3-[1-(2-chlorophenyl)methyl-2-propylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

A solution of 5-carboxymethyl-1-(2-chlorophenyl)methyl-2-propylthio-1H-imidazole (3.74 g, 11.5 mmol) in dry tetrahydrofuran (50 ml) was cooled to -78°C under argon, and a solution of diisobutyl aluminum hydride in toluene (30 ml of 1M) was added dropwise. The mixture was stirred at -78°C for 1.5 hours, then allowed to slowly warm to room temperature. The reaction was quenched by pouring onto iced dilute acetic acid, the product was extracted

into methylene chloride and the organic extracts were washed with water, 5% sodium carbonate solution and brine. The dried, concentrated product was a light tan solid (3.32 g). Crystallization from ethanol/water gave 1-(2-chlorophenyl)methyl-5-hydroxymethyl-2-propylthio-1H-imidazole; mp 98-101°C.

The title compound was prepared by the procedure of Example 1(iii and iv) using 1-(2-chlorophenyl)methyl-5-hydroxymethyl-2-propylthio-1H-imidazole in place of 2-n-butyl-1-(2-chlorophenyl)methyl-5-hydroxymethyl-1H-imidazole; mp 161-162°C.

Example 47

(E)-3-[[1-(2-Chorophenyl)methyl]-2-propenylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0108] The title compound is prepared following the procedure of Example 46 using allyl bromide in place of propyl bromide.

Example 48

(E)-3-[[1-(2-Chorophenyl)methyl]-2-pentylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0109] The title compound is prepared following the procedure of Example 46 using 1-bromopentane in place of propyl bromide.

Example 49

(E)-3-[[1-(2-Chorophenyl)methyl]-2-benzylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0110] The title compound is prepared following the procedure of Example 46 using benzyl bromide in place of propyl bromide.

Example 50

(E)-3-[[1-(2-Chorophenyl)methyl]-2-cyclohexylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0111] The title compound is prepared following the procedure of Example 46 using cyclohexyl bromide in place of propyl bromide.

Example 51

(E)-3-[[1-(2-Chorophenyl)methyl]-2-heptylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0112] The title compound is prepared following the procedure of Example 46 using 1-bromoheptane in place of propyl bromide.

Example 52

(E)-3-[[1-(2-Chorophenyl)methyl]-2-hexenylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0113] The title compound is prepared following the procedure of Example 46 using 6-bromo-1-hexene in place of propyl bromide.

Example 53

(E)-3-[[1-(2-Chorophenyl)methyl]-2-cyclopropylthio-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0114] The title compound is prepared following the procedure of Example 46 using cyclopropyl bromide in place of propyl bromide.

Example 54

(E)-3-[2-n-Butyl-1-[[2-chloro-4-(1H-tetrazol-5-yl)phenyl]methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0115] The procedure of Example 42 is followed using t-butyl 4-bromomethyl-3-chlorobenzoate (prepared from 3-chloro-4-methylbenzoic acid by esterification with 2-methylpropene in the presence of concentrated sulfuric acid, followed by methyl bromination with N-bromosuccinimide) in place of ethyl 4-bromomethyl-3-chlorobenzoate to give ethyl (E)-3-[2-n-butyl-1-[[2-chloro-4-(carbo-t-butoxy)phenyl]methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate. The t-butyl ester is converted to the corresponding acid compound using trifluoroacetic acid.

[0116] To a suspension of ethyl (E)-3-[2-n-butyl-1-[(2-chloro-4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propenoate in benzene is added thionyl chloride. The resultant mixture is heated to 50°C for 90 minutes, then evaporated to an oily residue. The residue is taken up in hexane and evaporated again. The acid chloride is treated with concentrated ammonium hydroxide and then the reaction mixture is stirred for 16 hours at room temperature. The solid is filtered, washed with water, and dried at 50°C under vacuum to yield the primary amide derivative.

[0117] To a solution of dimethylformamide in acetonitrile is added oxalyl chloride at 0°C under argon. After 3 minutes, a solution of the amide prepared above in dimethylformamide is added via a cannula. Five minutes later, pyridine is added; the reaction mixture is stirred for an additional 5 minutes at 0°C, then partitioned between ethyl acetate and 50% aqueous ammonium chloride. The ethyl acetate layer is washed with water and brine. The ethyl acetate extract is dried with anhydrous sodium sulfate and evaporated to give the corresponding nitrile derivative.

[0118] Tetrahydrofuran is added under argon with stirring to a mixture of the nitrile prepared above and aluminum chloride. Sodium azide is added all at once, followed by a tetrahydrofuran rinse, and the reaction is heated to 65°C for 22 hours, then cooled to room temperature. The reaction mixture is diluted with ethyl acetate and treated with 10% hydrochloric acid solution with vigorous stirring for 5 minutes. The ethyl acetate layer is washed with water and brine. The ethyl acetate layer is dried with anhydrous sodium sulfate and evaporated to give ethyl (E)-3-[2-n-butyl-1-[[2-chloro-4-(1H-tetrazol-5-yl)phenyl]methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate.

[0119] The title propenoic acid compound is prepared from the above ethyl ester by basic hydrolysis using aqueous base in methanol.

Example 55

(E)-[2-n-Butyl-1-[(2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0120] The title compound was prepared following the procedure of Example 1 using 2-nitrobenzyl bromide in place of 2-chlorobenzyl bromide; mp 205-206°C.

Example 56

(E)-[2-n-Butyl-1-[(3-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0121] The title compound was prepared following the procedure of Example 1 using 3-nitrobenzyl alcohol in place of 2-chlorobenzyl alcohol; mp 182-184°C.

Example 57

(E)-[2-n-Butyl-1-[(4-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0122] The title compound was prepared following the procedure of Example 42 using 4-nitrobenzyl bromide in place of ethyl-4-bromomethyl-3-chlorobenzoate; mp 198-200°C.

Example 58

(E)-[2-n-Butyl-1-[(2-trifluoromethylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0123] The title compound was prepared following the procedure of Example 1 using 2-trifluoromethylbenzyl alcohol in place of 2-chlorobenzyl alcohol; mp 202-203°C.

Example 59

(E)-[2-n-Butyl-1-[(2,3-dichlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0124] The title compound was prepared following the procedure of Example 1 using 2,3-dichlorobenzyl alcohol in place of 2-chlorobenzyl alcohol; mp 184-185°C.

Example 60

(E)-[2-n-Butyl-1-[(3-methoxy-2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0125] The title compound was prepared following the procedure of Example 42 using 3-methoxy-2-nitrobenzyl bromide in place of ethyl 4-bromomethyl-3-chlorobenzoate; mp 213-215°C.

Example 61

(E)-[2-n-Butyl-1-[(2-cyanophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0126] The title compound was prepared following the procedure of Example 1 using 2-cyanobenzyl bromide in place of ethyl 4-bromomethyl-3-chlorobenzoate; mp 210-212°C.

Example 62

(E)-[2-n-Butyl-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0127] The title compound was prepared following the procedure of Example 42 using 4-methoxy-3-methylbenzyl bromide in place of ethyl 4-bromomethyl-3-chlorobenzoate; mp 140-141°C.

Example 63

(E)-[2-n-Butyl-1-[(3-methoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0128] The title compound was prepared following the procedure of Example 1 using 3-methoxybenzyl alcohol in place of 2-chlorobenzyl alcohol; mp 170-171°C.

Example 64

(E)-[2-n-Butyl-1-[(2-methoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0129] The title compound was prepared following the procedure of Example 1 using 2-methoxybenzyl alcohol and methanesulfonic anhydride in place of 2-chlorobenzyl alcohol and triflic anhydride; mp 186-187°C.

Example 65

(E)-[2-n-Butyl-1-[(2-hydroxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0130] The title compound was prepared from the 2-methoxy compound prepared in Example 64 using boron tribromide in methylene chloride; 181-183°C.

Example 66

(E)-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methoxy-2-thienyl)methyl-2-propenoic Acid

[0131] The title compound was prepared by the procedure of Example 1 using 3-(5-methoxy-2-thienyl)-2-phosphonopropionate in place of 3-(2-thienyl)-2-phosphonopropionate; mp 184-185.5°C.

Example 67

(E)-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-methoxy-2-thienyl)methyl-2-propenoic Acid

[0132] The title compound was prepared by the procedure of Example 1 using 3-(4-methoxy-2-thienyl)-2-phosphonopropionate in place of 3-(2-thienyl)-2-phosphonopropionate; mp 170-171°C.

Example 68

(E)-3-[2-n-Hexyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thieny)methyl-2-propenoic Acid

[0133] The title compound was prepared following the procedure of Example 1, using caproylamidine methyl ether hydrochloride in place of valeramidine methyl ether hydrochloride and using 4-carbomethoxybenzyl alcohol in place of 2-chlorobenzyl alcohol; mp 210-212°C.

Example 69

(E)-3-[2-n-Propyl-1-[(2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0134] The title compound was prepared following the procedure of Example 1 using butyramidine methyl ether hydrochloride in place of valeramidine methyl ether hydrochloride and 2-nitrobenzyl alcohol in place of 2-chlorobenzyl alcohol; mp 223°C.

Example 70

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-[1-phenyl-1-(2-thienyl)phenylmethyl]-2-propenoic Acid

[0135] The title compound was prepared using the procedure of Example 1 (i, ii, iii, iv [Method B]) replacing methyl 3-(2-thienyl)propanoate with methyl 3-phenyl-3-(2-thienyl)propanoate [prepared as in Tetra. 44(7) 2055 (1988)]; mp 204-206°C.

Example 71

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-[2-phenyl-1-(2-thienyl)ethyl]-2-propenoic Acid

[0136] The title compound was prepared using the procedure of Example 1 (i, ii, iii, iv [Method B]) replacing methyl 3-(2-thienyl)propanoate with methyl 3-benzyl-3-(2-thienyl)propanoate [prepared following the procedure described in Tetra. 44 (7) 2055 (1988)]; mp 200-202°C.

Example 72

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-[1-(2-thienyl)pentyl]-2-propenoic Acid

[0137] The title compound was prepared using the procedure of Example 1 (i, ii, iii, iv [Method B]) replacing methyl 3-(2-thienyl)propanoate with methyl 3-(2-thienyl)heptanoate; mp 161-163°C.

Example 73

E-3-[2-n-Butyl-1-[(2-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0138] The title compound was prepared using the procedure of Example 42 replacing ethyl 4-bromomethyl-3-chlorobenzoate with ethyl 2-bromomethylbenzoate; 201-202°C.

Example 74

E-3-[2-n-Butyl-1-[(3-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0139] The title compound was prepared by the procedure of Example 1 (iv, Method B) using 2-n-butyl-1-[(4-carbo-

methoxyphenyl)methyl]imidazole-5-aldehyde (prepared by the method described for the preparation of 2-n-butyl-1-[(4-carboethoxy-2-chlorophenyl)methyl]-imidazole-5-aldehyde in Example 42) and methyl 3-(2-thienyl)propanoate; mp 243-244°C.

Example 75

(E)-3-[2-n-Butyl-1-[(4-hydroxy-3-methylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-pronenoic Acid

[0140] The title compound was prepared by demethylation of (E)-2-n-butyl-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared in Example 62, using boron tribromide in methylene chloride; mp 150-152°C.

Example 76

(E)-3-[2-n-Butyl-1-[(4-carbomethoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0141] The title compound was prepared using 2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]imidazole-5-aldehyde (prepared by the method described for the preparation of 2-n-butyl-1-[(4-carboethoxy-2-chlorophenyl)methyl]imidazole-5-aldehyde in Example 42) and t-butyl 3-(2-thienyl)-propanoate by the procedure of Example 1 (*iv*, Method B), except, instead of basic hydrolysis, trifluoroacetic acid hydrolysis of the t-butyl ester was employed; mp 217-220°C.

Example 77

(E)-3-[2-n-Butyl-1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0142] The title compound was prepared using 2-n-butyl-[(4-cyanophenyl)methyl]imidazole-5-aldehyde (prepared by the method of Example 42 describing the preparation of 2-n-butyl-1-[(4-carboethoxy-2-chlorophenyl)methyl]imidazole-5-aldehyde) and methyl 3-(2-thienyl)propanoate by the procedure of Example 1 (iv, Method B), except, instead of basic hydrolysis of the ester with sodium hydroxide, potassium carbonate hydrolysis was employed; mp 190-192°C.

Example 78

(E)-3-[2-n-Butyl-1-[(4-carbamoylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0143] Methyl (E)-3-[2-n-butyl-1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propanoate, prepared in Example 77, was subjected to hydrolysis with concentrated hydrochloric acid to give the title compound; mp 210-212°C.

Example 79

(E)-3-[2-n-Butyl-1-[[4-(1H-tetrazol-5-yl)-phenyl]methyl]-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propenoic Acid

[0144] The title compound was prepared from methyl (E)-3-[2-n-butyl-1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propanoate, prepared in Example 77, using the procedure described in Example 54; mp 246-248°C.

Example 80

(E)-3-[2-n-Propyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0145] The title compound was prepared using the procedure of Example 1 replacing valeramidine methyl ether hydrochloride with butyramidine methyl ether hydrochloride and replacing 2-chlorobenzyl alcohol with 4-carbomethoxybenzyl alcohol; mp 250°C (d).

Example 81

(E)-3-[2-n-Propyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0146] The title compound was prepared using the procedure of Example 1 replacing valeramidine methyl ether

hydrochloride with butyramidine methyl ether hydrochloride; mp 200°C.

Example 82

(E)-3-[2-n-Hexyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0147] The title compound was prepared using the procedure of Example 1 replacing valeramidine methyl ether hydrochloride with caproylamidine methyl ether hydrochloride; mp 161-163°C.

Example 83

(E)-3-[2-n-Butyl-1-[(4-carboxy-2,3-dichlorophenyl)methyl]1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0148] The title compound is prepared using the procedure of Example 42 replacing 4-bromomethyl-2,3-dichlorobenzoate (prepared by oxidation of 2,3-dichlorobenzoate (prepared by oxidation of 2,3-dichloro-p-xylene with nitric acid, followed by esterification with methanol/hydrochloric acid, and methyl bromination with N,N-bromosuccinimide).

Example 84

(E)-3-[2-n-Butyl-1-[(4-carboxy-2,5-dichlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0149] The title compound was prepared using the procedure of Example 42 replacing ethyl 4-bromomethyl-3-chlorobenzoate with methyl 4-bromomethyl-3,6-dichlorobenzoate (prepared by oxidation of 2,5-dichloro-p-xylene with nitric acid, followed by esterification with methanol/hydrochloric acid, and methyl bromination with N-bromosuccinimide).

Example 85

(E)-3-[2-n-Butyl-1-[(4-carboxynaphth-1-yl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

[0150] The title compound is prepared using the procedure of Example 42 replacing ethyl 4-bromomethyl-3-chlorobenzoate with 4-bromomethyl-carbomethoxynaphthalene (prepared by the oxidation of 1,4-dimethylnaphthalene with nitric acid, followed by esterification with methanol/hydrochloric acid, and methyl bromination with N-bromosuccinimide).

Example 86

(E)-3-[2-n-Butyl-1-[(2,3-dichlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenamide

[0151] (E)-3-[2-n-Butyl-1-[(2,3-dichlorophenyl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared in Example 59, was treated with thionyl chloride and then ammonium hydroxide, as described in Example 54, to give the title compound; mp 185-187°C.

Example 87

(E)-3-[2-n-Butyl-1-[(4-carbamoylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenamide

[0152] (E)-3-[2-n-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared in Example 41, was treated with thionyl chloride and then ammonium hydroxide, as described in Example 54, to give the title compound; mp 204-206°C.

Example 88

(E)-3-[2-n-Butyl-1-[(2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenamide

[0153] (E)-3-[2-n-Butyl-1-[(2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared in Example 55, was treated with thionyl chloride and then ammonium hydroxide, as described in Example 54, to give the title compound; mp 183-185°C.

Example 89

E-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propenoxy Acetic Acid

[0154] To a suspension of sodium hydride (53 mg, 2.3 mmol) in 5 mL of glyme was added portionwise (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenol (0.802 mg, 2.0 mmol, prepared as described in Example 17). After stirring for 30 minutes, methyl bromoacetate (3.35 mg, 2.2 mmol) was added dropwise. The reaction was stirred overnight at room temperature and then the mixture was poured into ice-water. The product was extracted into ethyl acetate (3x). The combined organic extracts were washed with water and brine and dried with anhydrous magnesium sulfate. The solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate (4:6) to give 2.44 mg (26%) of the ester of the title compound as an oil.

[0155] The ester was saponified by base as described in Example 1, iv, Method A(c); mp 141-142°C (ethyl acetate/methanol).

Example 90

E-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenyl Glycine

[0156] To a solution of (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid (0.5 g, 1.2 mmol prepared in Example 1) in tetrahydrofuran (12 mL) was added N-hydroxysuccinimide (0.153, 1.33 mmol), followed by dicyclohexylcarbodiimide (0.249 g, 1.2 mmol) in 5 mL of tetrahydrofuran. The reaction mixture was heated at 35°C for one hour and then glycine methyl ester hydrochloride (0.197 g, 1.57 mmol) and triethylamine (0.22 mL, 1.57 mmol) were added. The reaction was stirred at room temperature overnight. The mixture was diluted with 20 mL of ethyl acetate and the solids were filtered. The filtrate was concentrated to dryness and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (4:6) to give 0.258 g (44%) of the ester-amide as an oil.

[0157] The ester was saponified to the title acid compound by base, as described in Example 1 (iv, Method A(c); mp 175-177°C.

Example 91

(E-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenamide

[0158] (E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared in Example 1, was treated with thionyl chloride and then ammonium hydroxide, as described in Example 54, to give the title compound; mp 184-185°C.

Example 92

(E)-3-[2-n-Butyl-1-[(2-trifluoromethylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenamide

[0159] (E)-3-[2-n-Butyl-1-[(2-trifluoromethylphenyl)-methyl-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared in Example 58, was treated with thionyl chloride and then ammonium hydroxide, as described in Example 54, to give the title compound; mp 207-208°C.

Example 93

Ethyl (E)-3-[2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propanoate

[0160] The title compound was prepared following the procedure of Example 1 (iv, Method B) using 2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]imidazole-5-aldehyde, prepared by the method described for the preparation of 2-n-butyl-1-[(4-carboethoxy-2-chlorophenyl)methyl]-imidazole-5-aldehyde in Example 42, and ethyl 3-(2-thienyl)propanoate; mp 130-132°C.

Example 94

[0161] An oral dosage form for administering orally active Formula (I) compounds is produced by screening, mixing and filling into hard gelatin capsules the ingredients in proportions, for example, as shown below.

Ingredients	Amounts
(E)-3-[2-n-butyl-1-{(4-carboxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid	100 mg
magnesium stearate	10 mg
lactose	100 mg

Example 95

[0162] The sucrose calcium sulfate dihydrate and orally active Formula (I) compounds are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

Ingredients	Amounts
(E)-3-[2-n-butyl-1-{(4-carboxy-2-chlorophenyl)-methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid	75 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg
talc	4 mg
stearic acid	2 mg

Example 96

[0163] (E)-3-[2-n-Butyl-1-{(4-carboxy-3-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, 50 mg, is dispersed in 25 mL of normal saline to prepare an injectable preparation.

Example 97

[0164] A topical opthamological solution for administering Formula (I) compounds is produced by mixing under sterile conditions the ingredients in proportions, for example, as shown below.

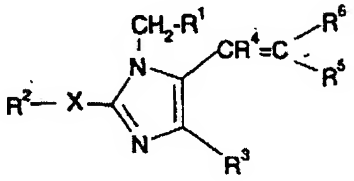
Ingredients	Amounts (mg/mL)
(E)-3-[2-n-butyl-1-{2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid	1.0
dibasic sodium phosphate	10.4
monobasic sodium phosphate	2.4
chlorobutanol	5.0
hydroxypropanol methylcellulose	5.0
sterile water	q.s.ad 1.0mL
1.0 N sodium hydroxide	q.s.ad pH 7.4

[0165] It is to be understood that the invention is not limited to the embodiments illustrated hereabove and the right

to the illustrated embodiments and all modifications coming within the scope of the following claims is reserved.

Claims

1. A compound of the formula (I):



(I)

in which:

R^1 is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_1-C_4 alkyl nitro, CO_2R^7, tetrazol-5-yl, C_1-C_4alkoxy, hydroxy, SC_1-C_4alkyl, SO_2NHR^7, $NHSO_2R^7$, SO_3H, $CONR^7R^7$, CN, SO_2C_1-C_4alkyl, or C_nF_{2n+1}, wherein n is 1-3;
R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_6cycloalkyl, or $(CH_2)_{0-3}$phenyl unsubstituted or substituted by one to three substituents selected from C_1-C_4alkyl, nitro, Cl, Br, F, I, hydroxy, C_1-C_4alkoxy, NR^7R^7, CO_2R^7, CN, or $CONR^7R^7$;
X is a single bond, S, or O;
R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, $COOR^7$, $CONR^7R^7$, NO_2, or C_nF_{2n+1}, wherein n is 1-3;
R^4 and R^5 are independently hydrogen, C_1-C_6alkyl, thienyl-Y-, furyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, pyridyl-Y-, or tetrazolyl-Y-, except that R^4 and R^5 are not both selected from hydrogen and 1-C_6alkyl and each heterocyclic ring is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, Cl, Br, F, I, NR^7R^7, CO_2R^7 SO_2NHR^7, SO_3H, or $CONR^7R^7$;
Y is a single bond, O, S, or C_1-C_6alkyl which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO_2, CF_3, C_1-C_4alkyl, C_1-C_4alkoxy, CN, or CO_2R^7;
R^6 is -Z-$COOR^8$ or -Z-$CONR^7R^7$;
Z is a single bond, vinyl, -CH_2-O-CH_2-, methylene optionally substituted by C_1-C_4alkyl, one or two benzyl groups, thienylmethyl, or furylmethyl, or -C(O)NHCHR^9-, wherein R^9 is H, C_1-C_6alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;
each R^7 independently is hydrogen, C_1-C_4alkyl, or $(CH_2)_m$phenyl, wherein m is 0-4; and
R^8 is hydrogen, C_1-C_6alkyl, or 2-di(C_1-C_6alkyl)-amino-2-oxoethyl; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which one of R^4 and R^5 is hydrogen or C_1-C_6alkyl.

3. A compound according to claim 1 or 2 in which:

R^1 is phenyl unsubstituted or substituted by one to three substituents selected from chloro, fluoro, trifluoromethyl, nitro, methyl, methoxy, hydroxy, sulfamido, carboxy, carboC_1-C_4alkoxy, carbamoyl, cyano, or tetrazol-5-yl;
X is a single bond;
R^2 is C_2-C_8alkyl;
R^3 is hydrogen, chloro, fluoro, or trifluoromethyl;
R^4 is hydrogen or C_1-C_6alkyl;
R^5 is thienylmethyl, furylmethyl, imidazolylmethyl, or pyridylmethyl, each of which is optionally substituted by methyl or methoxy; and
R^6 is COOH, $COOC_{1-2}$alkyl, or $CONH_2$.

4. A compound according to any one of claims 1 to 3 which is the E (trans) isomer.

5. A compound according to claim 1 which is:

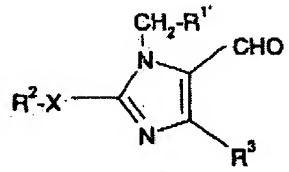
(E)-3-[2-n-butyl-1-{(4-carboxy-3-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(4-carboxy-2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(4-carbomethoxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-hexyl-1-{(4-carboxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-propyl-1-{(4-carboxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-nitrophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-furyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(4-imidazolyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-cyanophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(4-methoxy-3-methylphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methoxy-2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2,3-dichlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or
(E)-3-[2-n-butyl-1-{(2-trifluoromethylphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5 for use as a medicament.

7. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

8. A process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1, which process comprises:

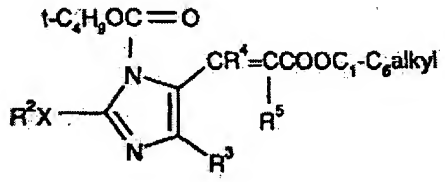
a) reacting a compound of the formula (II):



(II)

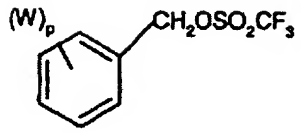
wherein R^2, R^3, and X are as defined in claim 1, and $R^{1'}$ as defined in claim 1, except that the substituents on the R^1 group do not include tetrazol-5-yl, OH, or CO_2H, with $(C_1\text{-}C_4\text{alkoxy})_2P(O)CH(R^5)\text{-}COOC_1\text{-}C_6\text{alkyl}$, wherein R^5 is as defined in claim 1, in the presence of a base; or

b) reacting a compound of the formula (III):



(III)

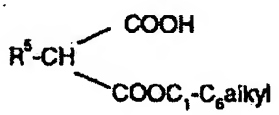
wherein R^2, R^3, R^4, R^5, and X are as defined in claim 1, with a compound of the formula (IV):



(IV)

wherein W is Cl, Br, F, I, C_1-C_4alkyl, nitro, CO_2C_1-C_4alkyl, C_1-C_4alkoxy, SC_1-C_4alkyl, CN, SO_2C_1-C_4alkyl, SO_2NHR^7, $NHSO_2C_1$-C_4alkyl, or C_nF_{2n+1}, n is 1-3, p is 0-3, and R^7 is hydrogen, C_{1-4}alkyl, or $(CH_2)_{0-4}$phenyl; or

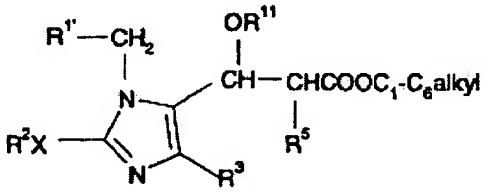
c) reacting a compound of the formula (II) as hereinbefore defined with a compound of the formula (V):



(V)

wherein R^5 is as defined in claim 1, in the presence of a base; or

d) reacting a compound of the formula (VI):



(VI)

wherein R^2, R^3, R^5, and X are as defined in claim 1, $R^{1'}$ is R^1 as defined in claim 1, except that the substituents on the $R^{1'}$ group do not include tetrazol-5-yl, OH, or CO_2H and R^{11} is $COCH_3$ or SO_2CH_3, with a base; or

e) reacting a compound of the formula (II) as hereinbefore defined with an appropriate heterocyclic acetic acid in acetic anhydride in the presence of a base;
and thereafter:

(i) for formula (I) compounds in which Z is $-CH_2-O-CH_2-$, reducing the formula (I) ester hereinbefore prepared, followed by reaction with a C_1-C_6alkyl haloacetate or;

(ii) for formula (I) compounds in which Z is $-C(O)NHCHR^9$ - wherein R^9 is H, C_1-C_4alkyl, phenyl, benzyl thienylmethyl, or furylmethyl, hydrolyzing the formula (I) ester compounds hereinbefore prepared, followed by reaction with an appropriately substituted amino acid, in the presence of an amide-forming reagent; or

(iii) for formula (I) compounds in which Z is a methylene group, reducing the formula (I) ester compounds hereinbefore prepared, followed by reaction with a C_1-C_6alkyl chloroformate and then reaction with carbon monoxide in the presence of a phosphine ligand; or

(iv) for formula (I) compounds in which Z is a methylene group substituted by C_1-C_4alkyl, benzyl, thienylmethyl, or furylmethyl, reacting the formula (I) ester compounds wherein Z is a methylene group prepared above with a lithium dialkylamide followed by reaction with an alkylating agent;
and thereafter where necessary:

(i) for formula (I) compounds in which the R^1 group is substituted by hydroxy, deprotecting the formula (I)

compounds in which the R^1 group is substituted by C_1-C_4alkoxy; or

(ii) for formula (I) compounds in which the R^1 group is substituted by carboxy, hydrolyzing the formula (I) compounds in which the R^1 group is substituted by CO_2C_{1-4}alkyl; or

(iii) for formula (I) compounds in which R^1 group is substituted by a tetrazol-5-yl group, treating the formula (I) compound in which the R^1 group is substituted by carboxy, with a halogenating agent, followed by conversion to the primary amide in a reaction with ammonia, dehydration with oxalylchloride/dimethylformamide and reaction with azide; or

(iv) for formula (I) compounds in which R^6 is -Z-COOH, hydrolyzing the formula (I) compounds in which R^6 is -Z-$COOC_1$-C_6alkyl; or

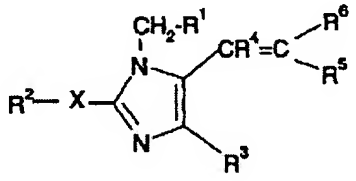
(v) for formula (I) compounds in which R^6 is -Z-$CONR^7R^7$ wherein R^7 is hydrogen, C_1-C_4alkyl, or $(CH_2)_{0-4}$phenyl, treating the formula (I) compounds in which R^6 is -Z-COOH with a halogenating agent, followed by reaction with an appropriately substituted amine;
and thereafter optionally forming a pharmaceutically acceptable salt.

9. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5 in the manufacture of a medicament for treatment of diseases in which angiotensin II receptor antagonism is a factor.

10. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5 in the manufacture of a medicament for the treatment of hypertension, congestive heart failure or renal failure.

Claims for the following Contracting States: ES, GR

1. A process for preparing a compound of the formula (I):



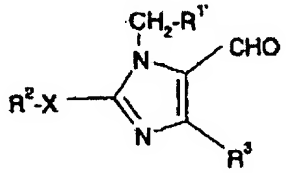
(I)

in which:

R^1 is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_1-C_4alkyl nitro, CO_2R^7, tetrazol-5-yl, C_1-C_4alkoxy, hydroxy, SC_1-C_4alkyl, SO_2NHR^7, $NHSO_2R^7$, SO_3H, $CONR^7R^7$, CN, SO_2C_1-C_4alkyl, or $C_n F_{2n+1}$, wherein n is 1-3;
R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_6cycloalkyl, or $(CH_2)_{0-8}$phenyl unsubstituted or substituted by one to three substituents selected from C_1-C_4alkyl, nitro, Cl, Br, F, I, hydroxy, C_1-C_4alkoxy, NR^7R^7, CO_2R^7, CN, or $CONR^7R^7$;
X is a single bond, S, or O;
R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, $COOR^7$, $CONR^7R^7$, NO_2, or C_nF_{2n+1}, wherein n is 1-3;
R^4 and R^5 are independently hydrogen, C_1-C_6alkyl, thienyl-Y-, furyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, pyridyl-Y-, or tetrazolyl-Y-, except that R^4 and R^5 are not both selected from hydrogen and C_1-C_6alkyl and each heterocyclic ring is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, Cl, Br, F, I, NR^7R^7, CO_2R^7, SO_2NHR^7, SO_3H, or $CONR^7R^7$;
Y is a single bond, O, S, or C_1-C_6alkyl which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO_2, CF_3, C_1-C_4alkyl, C_1-C_4alkoxy, CN, or CO_2R^7;
R^6 is -Z-$COOR^8$ or -Z-$CONR^7R^7$;
Z is a single bond, vinyl, $-CH_2-O-CH_2-$, methylene optionally substituted by C_1-C_4alkyl, one or two benzyl

groups, thienylmethyl, or furylmethyl, or -C(O)NHCHR^9-, wherein R^9 is H, C_1-C_6alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;
each R^7 independently is hydrogen, C_1-C_4alkyl, or $(CH_2)_m$phenyl, wherein m is 0-4; and
R^8 is hydrogen, C_1-C_6alkyl, or 2-di(C_1-C_6alkyl)-amino-2-oxoethyl; or a pharmaceutically acceptable salt thereof.
which process comprises:

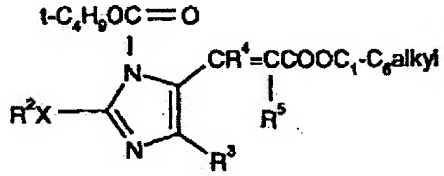
a) reacting a compound of the formula (II):



(II)

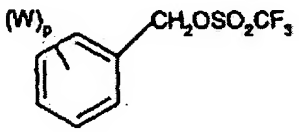
wherein R^2, R^3, and X are as defined in claim 1, and R$^{1'}$ as defined in claim 1, except that the substituents on the R^1 group do not include tetrazol-5-yl, OH, or CO_2H, with $(C_1$-C_4alkoxy$)_2P(O)CH(R^5)$-$COOC_1$-C_6alkyl, wherein R^5 is as defined in claim 1, in the presence of a base; or

b) reacting a compound of the formula (III):



(III)

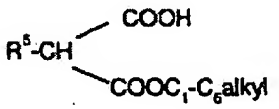
wherein R^2, R^3, R^4, R^5, and X are as defined in claim 1, with a compound of the formula (IV):



(IV)

wherein W is Cl, Br, F, I, C_1-C_4alkyl, nitro, CO_2C_1-C_4alkyl, C_1-C_4alkoxy, SC_1-C_4alkyl, CN, SO_2C_1-C_4alkyl, SO_2NHR^7, $NHSO_2C_1$-C_4alkyl, or C_nF_{2n+1}, n is 1-3, p is 0-3; and R^7 is hydrogen, C_{1-4}alkyl, or $(CH_2)_{0-4}$phenyl; or

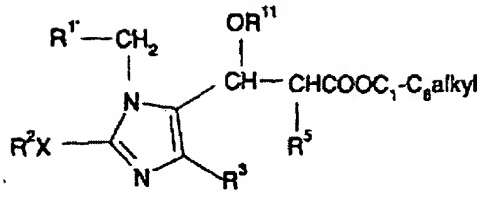
c) reacting a compound of the formula (II) as hereinbefore defined with a compound of the formula (V):



(V)

wherein R^5 is as defined in claim 1, in the presence of a base; or

d) reacting a compound of the formula (VI):



(VI)

wherein R^2, R^3, R^5, and X are as defined in claim 1, $R^{1'}$ is R^1 as defined in claim 1, except that the substituents on the $R^{1'}$ group do not include tetrazol-5-yl, OH, or CO_2H and R^{11} is $COCH_3$ or SO_2CH_3, with a base; or

e) reacting a compound of the formula (II) as hereinbefore defined with an appropriate heterocyclic acetic acid in acetic anhydride in the presence of a base;
and thereafter:

(i) for formula (I) compounds in which Z is $-CH_2-O-CH_2-$, reducing the formula (I) ester hereinbefore prepared, followed by reaction with a C_1-C_6alkyl haloacetate or;

(ii) for formula (I) compounds in which Z is $-C(O)NHCHR^9$ - wherein R^9 is H, C_1-C_4alkyl, phenyl, benzyl thienylmethyl, or furylmethyl, hydrolyzing the formula (I) ester compounds hereinbefore prepared, followed by reaction with an appropriately substituted amino acid, in the presence of an amide-forming reagent; or

(iii) for formula (I) compounds in which Z is a methylene group, reducing the formula (I) ester compounds hereinbefore prepared, followed by reaction with a C_1-C_6alkyl chloroformate and then reaction with carbon monoxide in the presence of a phosphine ligand; or

(iv) for formula (I) compounds in which Z is a methylene group substituted by C_1-C_4alkyl, benzyl, thienylmethyl, or furylmethyl, reacting the formula (I) ester compounds wherein Z is a methylene group prepared above with a lithium dialkylamide followed by reaction with an alkylating agent;
and thereafter where necessary:

(i) for formula (I) compounds in which the R^1 group is substituted by hydroxy, deprotecting the formula (I) compounds in which the R^1 group is substituted by C_1-C_4alkoxy; or

(ii) for formula (I) compounds in which the R^1 group is substituted by carboxy, hydrolyzing the formula (I) compounds in which the R^1 group is substituted by CO_2C_{1-4}alkyl; or

(iii) for formula (I) compounds in which R^1 group is substituted by a tetrazol-5-yl group, treating the formula (I) compound in which the R^1 group is substituted by carboxy, with a halogenating agent, followed by conversion to the primary amide in a reaction with ammonia, dehydration with oxalylchloride/dimethylformamide and reaction with azide; or

(iv) for formula (I) compounds in which R^6 is -Z-COOH, hydrolyzing the formula (I) compounds in which R^6 is -Z-$COOC_1$-C_6alkyl; or

(v) for formula (I) compounds in which R^6 is -Z-$CONR^7R^7$ wherein R^7 is hydrogen, C_1-C_4alkyl, or $(CH_2)_{0-4}$phenyl, treating the formula (I) compounds in which R^6 is -Z-COOH with a halogenating agent, followed by reaction with an appropriately substituted amine;
and thereafter optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 in which one of R^4 and R^5 is hydrogen or C_1-C_6alkyl.

3. A process according to claim 1 or 2 wherein:

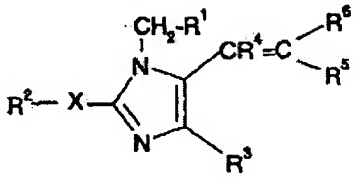
R^1 is phenyl unsubstituted or substituted by one to three substituents selected from chloro, fluoro, trifluoromethyl, nitro, methyl, methoxy, hydroxy, sulfamido, carboxy, carboC_1-C_4alkoxy, carbamoyl, cyano, or tetrazol-5-yl;
X is a single bond;
R^2 is C_2-C_8alkyl;
R^3 is hydrogen, chloro, fluoro, or trifluoromethyl;
R^4 is hydrogen or C_1-C_6alkyl;
R^5 is thienylmethyl, furylmethyl, imidazolylmethyl, or pyridylmethyl, each of which is optionally substituted by methyl or methoxy; and
R^6 is COOH, $COOC_{1-2}$alkyl, or $CONH_2$.

4. A process according to any one of claims 1 to 3 wherein the compound of formula (I) is the E (trans) isomer.

5. A process according to claim 1 wherein the compound of formula (I) is:

(E)-3-[2-n-butyl-1-{(4-carboxy-3-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(4-carboxy-2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(4-carbomethoxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-hexyl-1-{(4-carboxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-propyl-1-{(4-carboxyphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-nitrophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-furyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(4-imidazolyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methyl-2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-cyanophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(4-methoxy-3-methylphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]-2-(5-methoxy-2-thienyl)methyl-2-propenoic acid;
(E)-3-[2-n-butyl-1-{(2,3-dichlorophenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or
(E)-3-[2-n-butyl-1-{(2-trifluoromethylphenyl)methyl}-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or
a pharmaceutically acceptable salt thereof.

6. A compound of the formula (I):



(I)

in which:

R^1 is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_1-C_4alkyl, nitro, CO_2R^7 tetrazol-5-yl, C_1-C_4alkoxy, hydroxy, SC_1-C_4alkyl, SO_2NHR^7, $NHSO_2R^7$, SO_3H, $CONR^7R^7$, CN, SO_2C_1-C_4alkyl, or C_nF_{2n+1}, wherein n is 1-3;
R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_6cycloalkyl, or $(CH_2)_{0-8}$phenyl unsubstituted or substituted by one to three substituents selected from C_1-C_4alkyl, nitro, Cl, Br, F, I, hydroxy, C_1-C_4alkoxy, NR^7R^7, CO_2R^7, CN or $CONR^7R^7$;
X is a single bond, S, or O;
R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, $COOR^7$, $CONR^7R^7$, NO_2, or C_nF_{2n+1}, wherein n is 1-3;
R^4 and R^5 are independently hydrogen, C_1-C_6alkyl, thienyl-Y-, furyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, thiazolyl-Y-, pyridyl-Y-, or tetrazolyl-Y-, except that R^4 and R^5 are not both selected from hydrogen and C_1-C_6alkyl and each heterocyclic ring is unsubstituted or substituted by C_1-

C_4alkyl, C_1-C_4alkoxy, Cl, Br, F, I, NR^7R^7, CO_2R^7, SO_2NHR^7, SO_3H, or $CONR^7R^7$;
Y is a single bond, O, S, or C_1-C_6alkyl which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO_2, CF_3, C_1-C_4alkyl, C_1-C_4alkoxy, CN, or CO_2R^7;
R^6 is -Z-$COOR^8$ or -Z-$CONR^7R^7$;
Z is a single bond, vinyl, -CH_2-O-CH_2-, methylene optionally substituted by C_1-C_4alkyl, one or two benzyl groups, thienylmethyl, or furylmethyl, or -C(O)NHCHR^9-, wherein R^9 is H, C_1-C_6alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;
each R^7 independently is hydrogen, C_1-C_4alkyl, or $(CH_2)_m$phenyl, wherein m is 0-4; and
R^8 is hydrogen, C_1-C_6alkyl, or 2-di(C_1-C_6alkyl)-amino-2-oxoethyl; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6 for use as a medicament.

8. A pharmaceutical composition which comprises a compound according to claim 6 and a pharmaceutically acceptable carrier.

9. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 6 in the manufacture of a medicament for treatment of diseases in which angiotensin II receptor antagonism is a factor.

10. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 6 in the manufacture of a medicament for the treatment of hypertension, congestive heart failure or renal failure.

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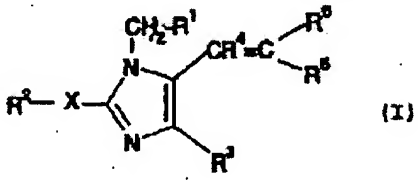
(54) Imidazolyl-alkenoic acid

(57) Angiotensin II receptor antagonists having the formula (I):



(I)

which are useful in regulating hypertension and in the treatment of congestive heart failure, renal failure, and glaucoma, pharmaceutical compositions including these antagonists, and methods of using these compounds to produce angiotensin II receptor antagonism in mammals.

EP 0 955 294 A3

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EUROPEAN SEARCH REPORT

Application Number
EP 99 11 5614

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	15 February 2000	Kyriakakou, G

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X : particularly relevant if taken alone
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L : document cited for other reasons

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